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ORIGINAL ARTICLES

SERUM COMPLEMENT IN CHILDREN WITH "COLLAGEN DISEASES"

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THE similarity between the lesions produced by the injection of foreign serum protein and those found in certain diseases (the so-called collagen and hypersensitivity diseases) in humans has suggested similar mechanisms of production[1] and has initiated many careful studies of experimentally-induced hypersensitivity in the hope that understanding of the sequence of events in the experimental animal might illuminate the pathogenesis of these diseases in the human.[2-4]

A close correlation between disappearance of circulating antigen, appearance of circulating antibodies, transient fall in the level of serum complement, and development of renal lesions exists in the experimental production of glomerular nephritis in the rabbit by massive injections of foreign serum protein. The depression of serum complement and the development of renal lesions are apparently dependent upon the production of antibodies. It has been suggested that this depression of serum complement is the *in vivo* counterpart of the binding of complement *in vitro* by the interaction of antigen and antibody.[5-8] This depression of serum complement during the *in vivo* antigen-antibody reaction in these experimental animals has led the authors to study levels of serum complement in children with so-called "collagen diseases."

Many such studies have been made in the past, but in most of them a semiquantitative technic has been used in which the amount of complement was estimated from the visible end point of complete hemolysis in a series of twofold dilutions. This technic cannot measure small changes, nor does it yield reproducible results. Much of the disagreement in the literature concerning serum complement in disease states can be ascribed to its

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inherent inaccuracies. The introduction of spectrophotometric technic for determination of the 50%-hemolytic end-point has given the investigator a better quantitative method for measurement of serum complement. This method will detect small changes, give reproducible results and has resolved many of the technical problems previously encountered.

The purpose of this paper is to present the results of determinations of serum complement by this quantitative method in 290 specimens of serum obtained from 70 children with disseminated lupus erythematosus, acute glomerular nephritis, the nephrotic syndrome, anaphylactoid purpura (Osler's syndrome[9]), dermatomyositis and rheumatoid arthritis.

Materials

Diluent: Throughout the determinations veronal®-buffered saline with added Ca^{++} and Mg^{++} was used. This was prepared by a modification of the formula of Mayer et al.*[10]

Sheep Cells: These were collected and "aged" in Alsever's solution, as described by Kabat and Mayer,[11] in a series of small flasks so that contamination from sampling could be minimized. Cells were prepared for use on day of titration by washing 3 times in cold buffered diluent, with centrifugation at 2000 rpm for 5 min. Final suspension was adjusted so that by lysing 1.0 cc. of RBC suspension with distilled H_2O 4.0 cc. a reading of 410 ± 10 was given on a Klett-Summerson colorimeter using a #54 (green) filter. This had been found to correspond to a concentration of 50×10^4 RBC/mm^3 in the original 1.0 cc. of suspension, or 10×10^4 RBC/mm^3 in final 5.0 cc. volume.

Hemolysin (Amboceptor): This was prepared in rabbits by usual method and titrated by method of Kent.[12]

Glassware: All glassware was washed in a detergent,† cleaned in acid-chromate solution, and rinsed initially in tap water, and finally in distilled water.

Methods

Collection of Samples: Sterile blood samples were taken by venipuncture from patients at Children's Medical Center, Boston. Blood was allowed to clot (usually in a refrigerator) and serum separated soon thereafter by centrifugation. Period during which sera were at room temperature was kept as short as possible, usually less than 1 to 2 hr. Sera were stored thereafter in paraffin-sealed heavy-walled test-tubes in a "dry-ice" box at —70°C. until day of titration. Whenever possible, all serial specimens from same patient were titrated on same day in order to increase comparative reliability of measurements of serum complement on same patient at different stages of his illness.

Measurement of Serum Complement: This was carried out by a 50%-hemolytic unit technic similar to that described by Kabat and Mayer.[11] Wherever possible, throughout the procedure, reagents and glassware were kept chilled, either in a refrigerator or in an ice-water bath.

Diluent was diluted 5-fold to isotonicity and chilled on day of titration. Erythrocytes were washed and brought to standard concentration. Ambocepter was diluted so that 1.0 cc. contained four 50%-hemolytic units (an excess) and equal volumes of amboceptor and red cell suspension were mixed, and allowed to stand at room temperature (*ca.*, 25°C.) for 15 min. Cells thus sensitized were then chilled. Sera to be titrated were removed from dry-ice box, allowed to thaw at room temperature, and appropriate dilutions were made. Dilutions depended upon expected range of serum complement, and varied from 1:5 for low-titre sera to 1:100 for high-titre sera. Usually a 1:40 dilution was used initially.

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* 5,5 diethyl barbituric acid 5.15 gm. was dissolved in hot H_2O 300 to 500 cc. and then allowed to cool. NaCl 85.5 gm., $NaHCO_3$ 0.25 gm., and Na 5,5-diethyl barbiturate 2.62 gm. were dissolved separately in cool H_2O about 500 cc. $MgCl_2 \cdot 6H_2O$ 1.0 gm. and $CaCl_2 \cdot 2\ H_2O$ 0.2 gm. were separately dissolved in cool H_2O 50 to 100 cc. in a 2000 cc. volumetric flask. Cool solution of NaCl, $NaHCO_3$ and sodium barbiturate was added and mixed. To this was added the cool barbituric acid and the total brought to 2000 cc. volume. Each day 1 part of this stock solution was diluted up to 5 parts with distilled water. Total molarity of this final solution calculated to 0.151M. with 0.00014 M Ca^{++} and 0.00049 M Mg^{++}. Measured pH was 7.4. Measured osmolarity by freezing-point determination was 280 mOsm/l.

† Alconox, Alconox Inc., Jersey City, N.J.

A series of calibrated Klett-Summerson test tubes were set up in racks in ice-water bath, and to each tube was added chilled sensitized red cell suspension 2.0 cc. Over red cell suspension chilled diluent was layered in amounts calculated so that diluent plus diluted serum plus red cell suspension gave a total volume of 5.0 cc. for entire system. Usually 3 tubes were used for each serum specimen, and to the 2.0 cc. of sensitized red cells was added 2.6, 2.4, and 2.1 cc. of diluent. Over these 2 layers was layered the diluted unknown serum, usually in quantities of 0.4, 0.6 and 0.9 cc. The total volume was thus 5.0 cc. Upon completion of pipetting and layering, contents of the tubes were rapidly and thoroughly mixed by inversion. Layering technic was used so that admixture of small amounts of complement with sensitized red cells during pipetting would not occur. Mixing was affected rapidly and at one time.

Tubes were then transferred to a water bath at 37 ± 0.5° C. and incubated with intermittent agitation for 30 min.

Following incubation tubes were again chilled in ice-water bath, and then centrifuged at 2000 rpm for 10 min. External surfaces of tubes were wiped dry and clean, and optical density of supernate determined on a Klett-Summerson Colorimeter, using a #54 (green) filter. Simultaneous control values for zero and 100% hemolysis were determined. From these percentages hemolysis for individual tubes was calculated.

The 50%-hemolytic unit titre of sera was calculated using the von Krogh formula ($x = [y/1-y]^n$) by method described by Mayer et al.[13] using log-log graph paper. This method was found satisfactory when 2 points were obtained to describe the line. Slope of line in normal ranges of titre was quite constant; however, with low-titered sera the slope increased. With low-titered sera, or especially with lipemic or turbid sera, the serum itself imparted color or turbidity to supernate irrespective of amount of hemolysis. Such interference gave erroneously high titres by increasing the measured optical density, and thus tended to give falsely high values.

Representative sera from all patients with low levels of serum complement were tested for anti-complementary activity, and no such activity was found.

Results

The level of serum complement during the active or initial stages of disseminated lupus erythematosus, acute glomerular nephritis, the nephrotic syndrome, anaphylactoid purpura, dermatomyositis and rheumatoid arthritis (including Still's disease) was determined in 70 patients and compared with the normal range (Fig. 1). In addition, serial complement determinations were made during the natural or therapeutically altered course of these diseases.

1. The "Normal" Range: In 52 apparently normal individuals serum complement was determined. The mean value was found to be 47.7 $U_{50\%}$.* The standard deviation from the mean was ± 13.3 $U_{50\%}$.

2. Disseminated Lupus Erythematosus: The initial serum complement values in four patients with disseminated lupus erythematosus were found to be below the normal range (mean of initial titres: 15 $U_{50\%}$), and in 62 specimens of serum obtained from these four patients during the course of their disease a diminished serum-complement titre was always found. In 2 of the 4 patients serial determinations of serum complement were made over a period of several months. During this period various therapeutic measures were taken to induce remissions. Initially a course of ACTH therapy was given to both patients. A remission occurred in each case, and during remission the abnormally low serum-complement titre rose, although not to normal levels, only to fall again, during the subsequent relapses (Fig. 2). It should be noted that during remissions the hematuria and albuminuria initially observed remained unaltered. Subsequent to ACTH therapy both of these patients were given nitrogen mustards,† and again a temporary remission

* Throughout the abbreviation $U_{50\%}$ is used to indicate 50% hemolytic units/cc. undiluted serum.

† 0.6 mg./kg. of methyl bis (chloro ethyl) amine HCl in 2 doses, given 48 hr. apart.

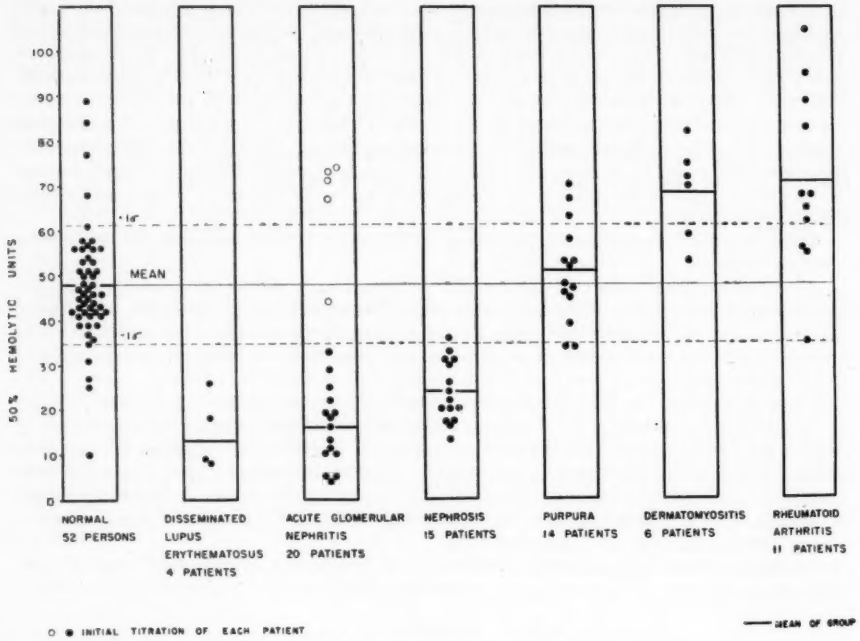

FIG. 1. Initial complement titres of 70 patients with diseases studied, compared to normal range in 52 apparently normal individuals.

was apparently induced. Finally both patients were given a course of cortisone therapy. Neither of these last two agents produced any definite change in the serum-complement titres in the two patients. The nitrogen mustards induced a brief (24 hour) decrease in the urinary excretion of protein and formed elements, while during the administration of cortisone, proteinuria increased in both patients.

3. Acute Glomerular Nephritis: Sera obtained from 15 patients during the initial active phase of this disease were tested, and the serum complement was found to be diminished below the range of normal (mean of initial titres: 16 $U_{50\%}$). In addition, the serum complement was estimated in five patients in whom the initial diagnosis of acute glomerular nephritis is open to question. (The initial titres on these five patients are indicated by open circles in the third column of Fig. 1.) One of these patients had had hematuria for 10 days before the serum sample was obtained, but within three days after the sample was drawn, hematuria had ceased. The disease was apparently subsiding at the time the titre was determined. Two patients had a history of previous episodes that suggested hematuria, and thus may perhaps have had exacerbation of an old nephritis, rather than an acute initial attack. In the two remaining patients there was only transient hematuria without cylindruria or other manifestations of acute glomerular nephritis.

In 8 of the 15 patients with low serum-complement values during the initial active phase of the disease, serial determinations were made during the course of the disease and subsequent convalescence. In each case, the initial low serum-complement titre rose

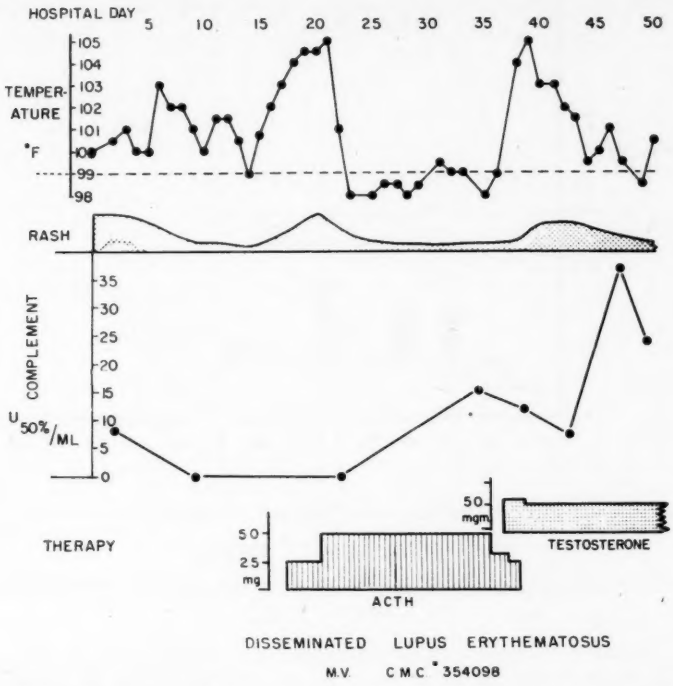

FIG. 2. Course of serum complement in 7½ yr. old girl with disseminated lupus erythematosus. Note rise in serum complement during remissions induced with ACTH and testosterone therapy. High fever between 35th and 40th days of obscure origin may represent "rebound" from withdrawal of ACTH, exacerbation, or intercurrent infection; one blood culture was positive for Staph. aureus hemolyticus. This episode of "stress" may have contributed to rise in serum complement.

as the urine cleared (Fig. 3) and, by the time the symptoms and signs of the disease had disappeared, serum complement had returned to a normal level.

4. Nephrotic Syndrome: In 15 patients in the edematous stage, the initial serum-complement titre was found to be below the normal range (mean of initial titres: 24 $U_{50\%}$). Serial determinations were obtained in 12 of these 15 patients. None of them experienced spontaneous remission or diuresis during the period of observation, and complement levels remained consistently below the normal range while in the edematous stage of the disease. Ten of these patients were given ACTH therapy in an attempt to induce a diuresis. The change in renal hemodynamics of these same patients has been previously reported by Metcoff and his associates.[14] In addition to these changes it was found that when a diuresis was induced the serum-complement titre rose rapidly to the normal range. The rapid increase in this initially-diminished serum-complement level occurred concomitantly with and, on occasion, possibly just before the onset of the marked diuresis induced by this hormone. The increase in the serum-complement titre bore no relation to measured changes in the daily urinary-protein excretion, and occurred in spite of an increase in proteinuria (Fig. 4) as well as when the proteinuria decreased (Fig. 5). Such a return of serum complement to normal levels occurred in eight patients

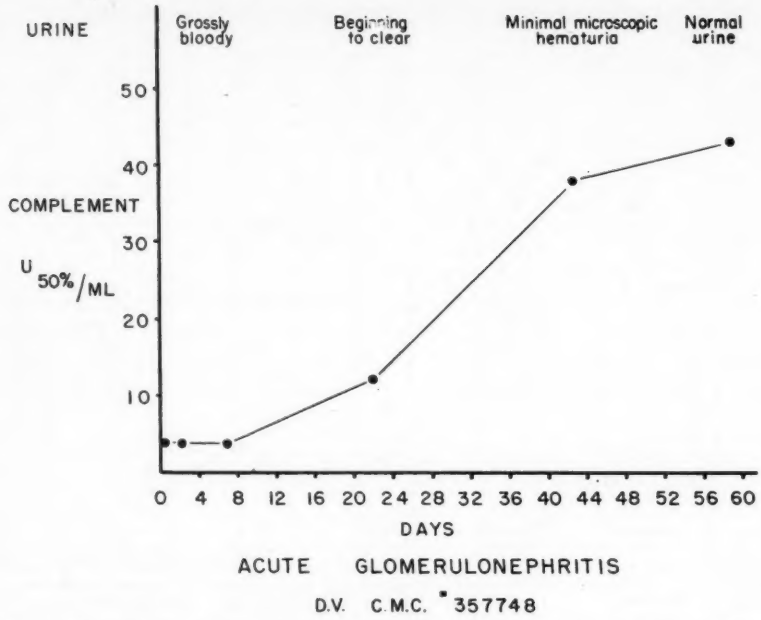

FIG. 3. Course of serum complement in $5^{10}/_{12}$ yr. old patient with acute glomerulonephritis.

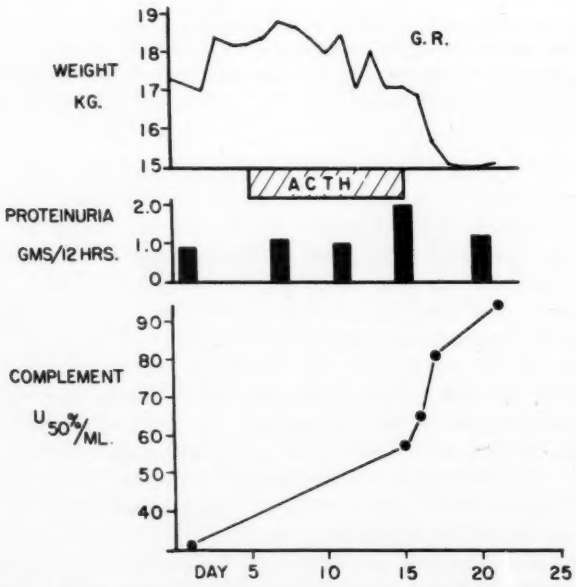

FIG. 4. Behaviour of serum complement in patient with nephrotic syndrome in whom ACTH therapy induced diuresis. There was no decrease in proteinuria while serum-complement level rose.

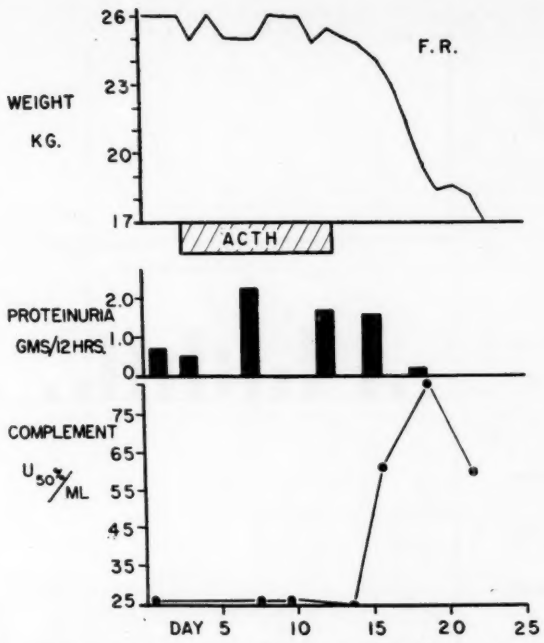

FIG. 5. Course of serum complement in patient with nephrotic syndrome, in whom ACTH therapy induced diuresis. In this case there was decrease in proteinuria, with increase in serum complement.

in whom ACTH therapy induced a diuresis. In two patients, in whom ACTH therapy did not induce a diuresis, no change in serum complement titre was observed.

5. Anaphylactoid Purpura: The sera of 14 patients with nonthrombocytopenic purpura, with and without arthralgia, melena and hematuria were obtained during the initial active phases of the disease. The serum-complement titres of these patients were all within normal range, although the mean titre (51 U_{50}%) was slightly above the normal mean. Only three of the patients were followed serially, and in none was any definite trend or change in the serum-complement titre demonstrable. Two of the patients, who had purpura, arthralgia, melena and hematuria with proteinuria, were given ACTH therapy. In neither patient was the clinical response dramatic. In one, during therapy (Fig. 6) there was a decrease in hematuria with an increase in proteinuria. During this period the patient became edematous. The serum-complement titre remained within the normal range.

6. Dermatomyositis: In six patients with dermatomyositis, the initial serum-complement titres during the active phase of the disease were all found to be above the mean of the normal group (mean of initial titres 68 $U_{50\%}$). Three of these patients were followed serially. In one, the serum-complement titre fell from the high initial titre to a normal level during a course of ACTH therapy (Fig. 7). The other two patients (who were, incidentally, twins) showed a similar return of the serum value toward the normal during spontaneous remissions.

7. Rheumatoid Arthritis: Eleven patients with active rheumatoid arthritis or Still's disease were found to have elevated values for serum complement during the initial

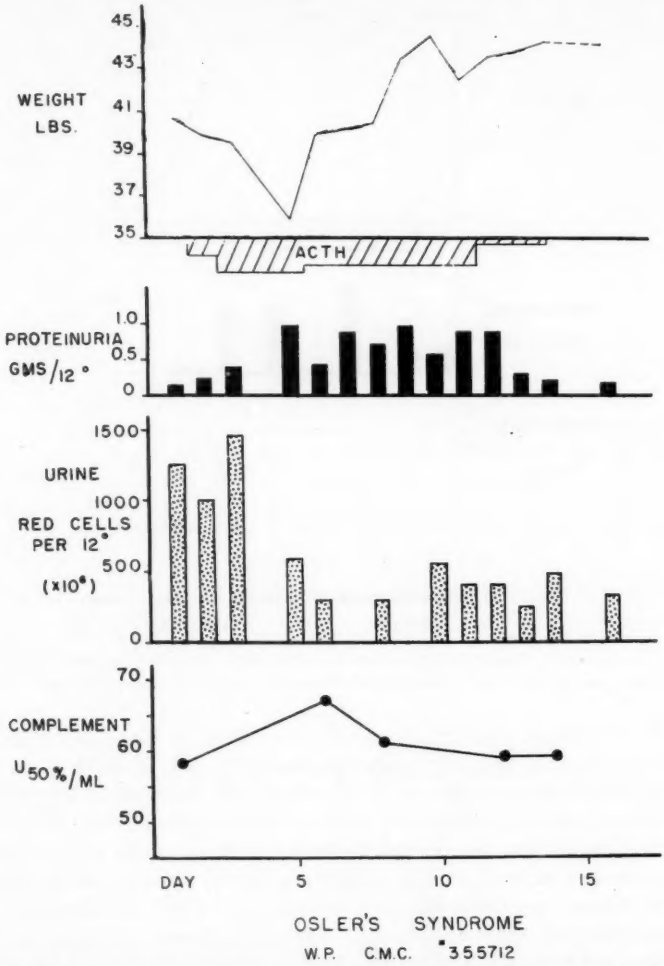

FIG. 6. Behaviour of serum complement in 3 yr. old patient with anaphylactoid purpura during ACTH therapy. Note increase in proteinuria and weight during therapy, without any significant changes in serum complement.

active phase of the disease. The mean titre (71 $U_{50\%}$) was well above the normal range, as were the majority of the individual titres. This abnormally-elevated titre returned to the normal range in two patients in whom ACTH therapy induced a remission (Fig. 8). In one patient, 20 months of age, with a particularly acute febrile form of the disease, ACTH therapy did not produce any marked effect, and the serum complement titre did not return to the normal level.

DISCUSSION

1. The Normal Range: The mean titre for the normal individuals in this series differs from that reported by Fischel.[15] The variance between these two means can be ascribed

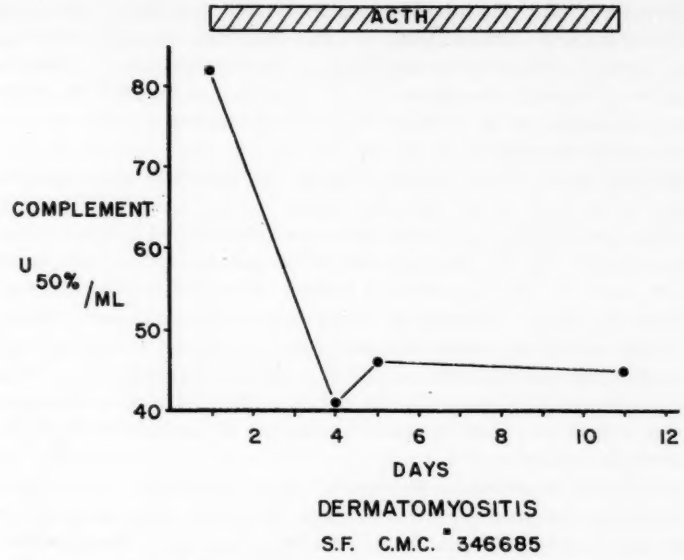

FIG. 7. Serum complement during ACTH therapy in 5 yr. old girl with dermatomyositis. Note return to normal levels of serum complement.

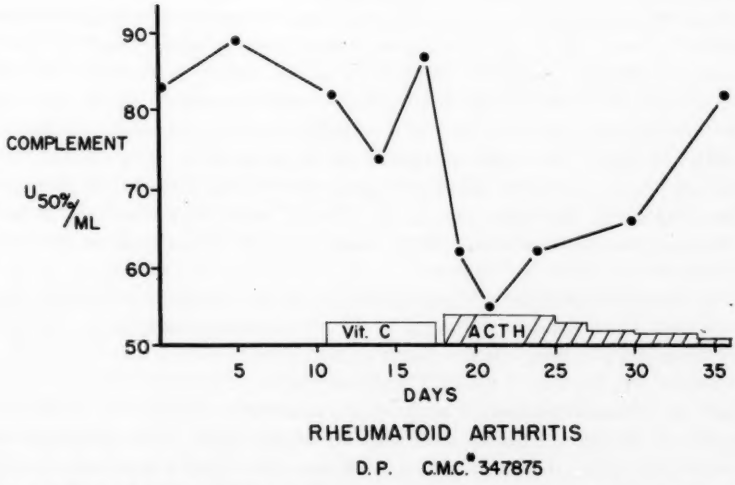

FIG. 8. Course of serum complement during ACTH therapy in 3 yr. old boy with severe febrile rheumatoid arthritis. During first week of therapy marked clinical improvement was associated with return of serum complement towards normal level. However as ACTH dosage was decreased, serum complement began to rise, reaching same level at time therapy was discontinued that it had been before therapy. Patient likewise had profound clinical relapse when therapy was discontinued, and was no better at end of therapy than at its start.

to the difference in total volume used during the titration procedure. Differences in titre of the same serum with different volumes in the system used during titration have been reported by Mayer[16] and, using this data to correct for this difference in technic, the mean of this series is found to be essentially the same as that reported by Fischel. The difference in the range of the standard deviation from the mean cannot be corrected in this manner and is unexplained.

2. Disseminated Lupus Erythematosus: The low titres presented are in agreement with the findings of Vaughan et al.[17] as is the increase in titre during ACTH therapy. The decrease in urinary excretion of protein and former elements and the clinical improvement observed following the administration of nitrogen mustards to two patients with disseminated lupus has been described in patients with chronic glomerulonephritis by Chasis and his associates.[18] However, the behavior of serum complement in these patients did not correspond to what might have been expected from the present authors' studies on the effects of nitrogen mustards and ACTH on experimental nephritis on rabbits due to foreign protein.[6, 7] The increase in proteinuria of the two patients during cortisone administration might have some relationship to the specific renal lesions found in rabbits given cortisone by Rich's group.[19]

3. Acute Glomerular Nephritis: Diminished serum complement in acute glomerular nephritis has been described previously[20–26] and the rise in titre during the recovery period has been noted by these authors. The data presented in these patients would suggest that the measurement of serum complement may aid in differentiating various hemorrhagic nephropathies, which was suggested by Kellett in 1936,[20] and more recently by Fischel and Gajdusek.[26] In addition, the parallelism of the serum-complement titre and the clinical findings in the course of the disease might allow the use of the titre to follow the activity of the disease in the patient once the diagnosis is substantiated.

4. Nephrotic Syndrome: Lange[25] and Fischel[26] have reported similar diminished serum-complement titres to those found in the patients in this series. The low titres (as mentioned under *Methods*) cannot be ascribed to turbidity of the sera, nor to anticomplementary activity. The rise in titre at the onset of diuresis induced by ACTH suggests that the determination might be used as a prognostic guide under similar circumstances.

5. Other Diseases: The slightly elevated serum-complement titres in the cases of anaphylactoid purpura agree essentially with those described by Fischel.[26] In patients with dermatomyositis and rheumatoid arthritis the definitely increased levels of serum complement are of a similar magnitude to those found in active rheumatic fever by Fischel[15] and in rheumatoid arthritis by Vaughan.[27]

Kellett[20] in 1936 stated that "if gross antibody-antigen reactions are taking place in the body, then there should be changes in the complement content of the blood, and that the recognition of these changes would in turn provide evidence as to the existence of antibody-antigen reaction in man." The demonstration of this relationship in the production of experimental glomerular nephritis in the rabbit[5–8] supports this hypothesis, as do the data of Fischel and Benacerraf,[28] who demonstrated that, although fatal anaphylaxis can be produced in the guinea pig by small doses of antigen without any demonstrable decrease in serum complement, when larger doses are used with severe or fatal anaphylaxis the serum complement falls dramatically. The low serum-complement titres found in these patients with disseminated lupus erythematosus, acute glomerular nephritis and the nephrotic syndrome are best explained on this basis and provide some, but certainly not conclusive, evidence for the allergic nature of these diseases. It does not seem valid

to attempt to explain the decreased complement levels through loss of protein in the urine in spite of the demonstration of components of complement in urinary protein[29] because, as other authors have pointed out,[23, 26] there is no correlation between the extent of urinary-protein excretion and the level of serum complement. In the nephrotic syndrome during diuresis, the complement titre may rise in spite of an increase in proteinuria; and in patients with other renal diseases with marked proteinuria (anaphylactoid purpura, recurrent subacute chronic nephritis), normal or slightly elevated serum-complement titres have been found.

No evidence of anticomplementary activity in the sera of these patients with diminished serum complement could be demonstrated. That there might be a deficiency or decreased production of serum complement does not seem likely.

The elevated serum complement titres in anaphylactoid purpura, dermatomyositis, rheumatoid arthritis and rheumatic fever cannot be explained on the basis of *in vivo* fixation of complement by an antigen-antibody reaction, but do not preclude an immunologic mechanism in the pathogenesis of these diseases. That immunologic reactions can occur without a decrease in serum complement has been demonstrated and discussed by Fischel.[15, 28] It seems more reasonable to suggest that the decreased and elevated titres may be evidence of differences between these diseases, differences in the immunologic reactions. These might be the result of differences in the relative amounts of antigen or antibody involved in the reaction, in the type of antigen or antibody involved, in the presence and location of antigen or antibody fixed in the tissues, or in the time relationships between the stimulus and the reaction.

Summary

The complement titres of 290 specimens of serum taken from 70 patients with disseminated lupus erythematosus, acute glomerular nephritis, the nephrotic syndrome, anaphylactoid purpura, dermatomyositis and rheumatoid arthritis were determined by the spectrophotometric technic using the 50% hemolytic end-point. These titres were compared to the normal range, and changes in titre during the natural and therapeutically-altered course of these diseases were studied.

Serum complement was found to be diminished in disseminated lupus erythematosus, acute glomerular nephritis and the nephrotic syndrome. In anaphylactoid purpura the titres were possibly slightly elevated and in dermatomyositis and rheumatoid arthritis, they were markedly elevated. During natural or induced remissions the abnormal titres returned toward the normal range.

These findings are discussed in relation to experimental work and present hypotheses of the pathogenesis of these diseases.

Acknowledgment

The authors are indebted to the House Staff of the Children's Medical Center, without whose cooperation these studies could not have been performed, and to Dr. Henry G. Carleton who, with the authors in 1946, helped to develop the method of titration used in this study.

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SPANISH ABSTRACT

Complemento del Suero en Niños con "Enfermedades del Colágeno"

En la producción experimental de la nefritis glomerular del conejo por inyecciones masivas de proteínas séricas extrañas, hay una correlación íntima entre la desaparición del antígeno circulante, la aparición de anticuerpos circulantes, la caída transitoria del nivel del complemento del suero y el desarrollo de lesiones renales. La depresión del complemento del suero y el desarrollo de las lesiones renales aparentemente dependen de la producción de anticuerpos. Se ha sugerido que esta depresión del complemento es una duplicación "in vivo" del aprisionamiento o fijación del complemento "in vitro" por la interacción del antígeno y anticuerpo. Esta depresión del complemento del suero durante la reacción antígeno-anticuerpo en estos animales de experimentación llevó a los autores de este artículo a estudiar los niveles del complemento del suero en niños con las denominadas enfermedades del colágeno.

Con esta idea determinaron los títulos del complemento de 290 especímenes de suero tomados de 70 niños con lupus eritematoso diseminado, nefritis glomerular aguda, síndrome nefrótico, púrpura anafilactoide, dermatomiositis y artritis reumatoide, por medio de la técnica espectrofotométrica usando el 50% de hemólisis punto final.

Estos títulos fueron comparados con las variaciones normales y estudiados en sus variaciones durante las modificaciones naturales y terapéuticas de estas enfermedades.

El complemento del suero se encontró disminuido en el lupus eritematoso diseminado, nefritis aguda glomerular y el síndrome nefrótico. En la púrpura anafilactoide los títulos estaban posiblemente ligeramente elevados y en la dermatomiosítis y artritis reumatoide estaban marcadamente altos. Durante las remisiones inducidas o naturales los títulos anormales regresaron a los límites normales.

Los autores aceptan la afirmación de Kellet de que "si en el cuerpo se estan realizando reacciones antígeno-anticuerpo toscas, entonces debe haber cambios en el contenido de complemento de la sangre y la demonstración de estos cambios daría a su vez pruebas de la existencia de la reacción antígeno-anticuerpo en el hombre," y creen que la demostración de esta correlación en la producción experimental de la nefritis glomerular en el conejo respalda dicha hipótesis así como la demostración de que aunque se puede producir una anafilaxis fatal en el cobayo por pequeñas dosis de antígeno sin ningún descenso demostrable del complemento del suero, cuando se usan dosis más grandes con anafilaxis severa o fatal, el complemento del suero cae dramáticamente. Creen que los bajos títulos del complemento del suero encontrados en los pacientes con lupus eritematoso diseminado, glomerulonefritis aguda y el síndrome nefrótico son explicados mejor sobre estas bases y dan cierta evidencia, aunque ciertamente no concluyente, de la naturaleza alérgica de estos padecimientos.

Eliminan la posibilidad de que el descenso de los títulos de complemento sea debida a la proteinuria o a actividad anticomplementaria del suero de los pacientes, la cual no pudo ser demostrada, y piensan que no sea probable una deficiencia o producción disminuida de complemento del suero.

Los títulos elevados del complemento del suero en la púrpura anafilactoide, dermatomiositis, artritis reumatoide y fiebre reumática no pueden ser explicadas sobre las bases de fijación de complemento "in vivo" por una reacción antígeno-anticuerpo pero no excluye un mecanismo inmunológico en la patogénesis de estas enfermedades como ha sido discutido y demostrado por Fischel quien acepta que pueden ocurrir reacciones inmunológicas sin descenso del complemento del suero.

A los autores del trabajo les parece más razonable que la disminución o aumento de los títulos pueda ser la prueba de diferencias entre estas enfermedades, diferencias en las reacciones inmunológicas. Estas pueden ser el resultado de diferencias en las cantidades relativas de antígeno o anticuerpo involucradas en las reacción, en el tipo de antígeno o anticuerpo, en la presencia y localización del antígeno o anticuerpo fijado en los tejidos o en las relaciones de tiempo entre el estímulo y la reacción.

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FUNNEL CHEST

Indications for Surgery and the Time of Choice for Operation

By ALEXANDER H. BILL, JR., M.D.
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FUNNEL chest is a deformity seen frequently in both children and adults. It rarely causes disability in children. When patients reach maturity a lack of definite information exists as to whether the deformity is injurious to health.

This study proposes to investigate the status of patients in later life in relation to whether operation should be suggested in childhood.

The study is based upon an analysis of a questionnaire as to the fate of adult patients with untreated funnel chest submitted to a group of physicians and surgeons with wide experience in diseases of the chest. It is also based upon observation of eight children who have been operated upon by the author.

There is a depression of the lower two-thirds of the sternum in the usual severe grade of this deformity, with the lower 4 or 5 costal cartilages extending backward from the rib ends to their juncture with the sternum (Fig. 1). The tip of the sternum may be depressed so far as to actually touch the vertebral bodies. Usually the heart is deflected toward the left.

REVIEW OF LITERATURE

The literature contains a number of reports in which the authors feel that there is a cardiac disability associated with a severe grade of funnel chest. Brodkin[1] reports 6 patients in 4 of whom he found tachycardia when they were standing, together with shortness of breath and sometimes precordial pain. Ravitch[2] describes a 28 year old man with auricular fibrillation and heart failure who improved after operation. Ochsner and DeBakey[3] report a 30 year old patient with cyanosis and precordial pain. Brown and Cook[4] state that many of the older patients have respiratory symptoms, and also cardiac impairment. Lester[5] believes that most patients have functional murmurs and that some have cardiac symptoms.

Several other studies have been made. Evans[6] studied 16 patients with a suspicion of heart disease associated with funnel chest. He came to the conclusion that most of these patients were invalids because of medical advice to limit their activities rather than because of any real heart impairment. Sutton[7] studied two adults, one of whom was asymptomatic while the other died of heart failure with no findings other than the funnel chest deformity to account for the death. Edeiken and Wolferth[8] studied 10 cases. In five of these, 17 years of age and under, they found no symptoms or signs of cardiac disability. In five cases, 19 years of age and older, they found four with indications of cardiac disability including paroxysmal fibrilation, severe precordial pain, low blood pressure and weakness, and dyspnea and cyanosis. Master and Stone[9] studied 25 patients with funnel-

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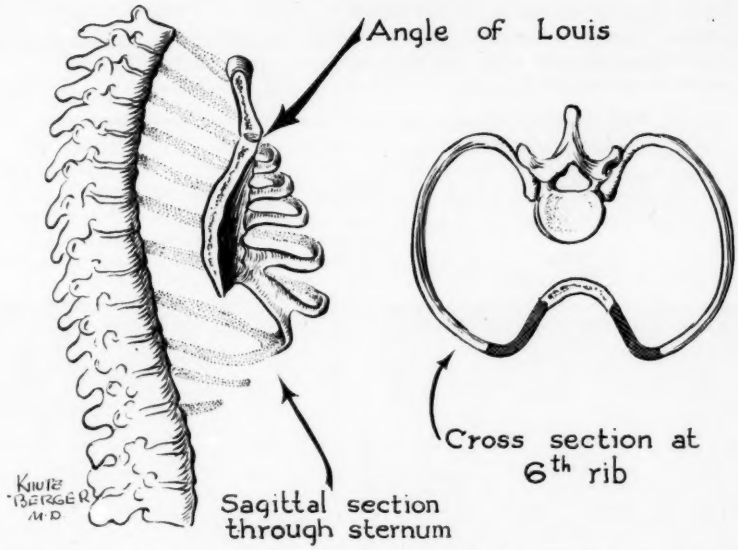

FIG. 1. Bony deformities in severe degree of funnel chest.

shaped and flat chests in adult life. All of these had some cardiac signs, such as tachycardia or murmur. The diagnosis of neurocirculatory asthenia was made in 16 patients. Hutcheson[10] studied six adult patients and made a diagnosis of neurocirculatory asthenia in three.

RESULTS OF QUESTIONNAIRE

Because of widespread uncertainty as to the fate of patients in later life and as to the indications for operation, the author, with the help of Dr. Byron F. Francis of Seattle, circulated a questionnaire to a group of American surgeons and physicians. The questionnaire asked what proportion of patients with severe degree of funnel chest develop: (a) cardiac disability, (b) pulmonary disability, (c) psychologic disability. In addition it asked whether the life span of such patients is shortened. Lastly the question was put as to whether operative repair in childhood should be advised. Twenty-five questionnaires were answered completely enough to be useful.

Table 1 shows that the majority of those questioned believe that some of the patients suffer from cardiovascular disability. There was a similar feeling about pulmonary disability. Fourteen answers indicated that some proportion of these cases are bothered by a psychologic handicap, while 5 indicate that this factor is unimportant. Opinion is evenly divided as to whether the life span is shortened by an uncorrected severe degree of the deformity.

As to the question whether operation should be suggested in childhood for a patient with severe deformity, there is more uniformity of opinion. Twenty-three believe that early operation should be suggested, while two are undecided. Three who feel that early surgery should be done are inclined to reserve the operation for girls.

TABLE 1

TABULATION OF ANSWERS TO QUESTIONNAIRE CONCERNING FUNNEL CHEST, SUBMITTED TO GROUP OF AMERICAN PHYSICIANS WITH WIDE EXPERIENCE IN DISEASES OF CHEST

1. What proportion of adults with severe funnel chest deformity develop:			
a. Cardiac disability:			
"Some"	13		
100%	2	Yes	16
75%	1		
None	7	No	7
No opinion	2		
b. Pulmonary disability			
"Some"	8		
100%	2	Yes	13
"Majority"	3		
None	8	No	8
No opinion	4		
c. Psychologic disability			
"Majority"	7		
100%	4	Yes	14
"Some"	3		
None	5	No	5
No opinion	6		
2. Will the presence of severe funnel chest shorten the life span?			
		Yes	9
		No	10
No opinion	6		
3. Should a severe grade of funnel chest be repaired in childhood?			
		Yes	23
		No	0
No opinion	2		

SURGICAL TREATMENT

Two general types of surgery have been recommended during the past few years. These have been variations of the surgical procedures described by Brown.[11] The first procedure, which he calls a "simple" operation and which he recommends for infants, is that of freeing the inner surface of the lower portion of the sternum from its posterior attachments. The second procedure, which had previously been described by Garnier,[12] consists of the removal of the backward-projecting segments of the lower costal cartilages together with the performance of a wedge osteotomy across the upper sternum to permit the sternum to come forward. Varying modifications of this latter operation include: resuturing the rib ends to the sternum,[13] using a transplanted-bone strut to hold the sternum forward[14-17] and various temporary methods of traction through the skin to maintain the sternum in the correct position during healing.

Of the author's 8 cases, 2 were operated upon by the so-called "simple" technic of Brown. These 2 patients were infants, 6 mo. and 10 mo. of age, and little improvement has been noted in either case.

In connection with these 2 disappointing results it should be pointed out that in 7 of the author's cases it was not possible to identify any tight ligamentous structure (the so-called "substernal ligament") such as had been described by Brown, extending from the lower sternum toward the diaphragm. In one case only were firm tissues found behind the lower sternum. Because of these facts the author has given up this type of operation.

Six cases have been operated upon by the more radical technic. Of these operations 3 were done more than 1 yr. ago and show excellent continuing results. The ages of these 3 children at the time of surgery were 2 yr. in 2 cases and 3 yr. in the third (Fig. 2). Two recent procedures on children have had satisfactory immediate results but there has not been a long enough follow-up period for evaluation. One 15 yr. old boy was operated upon recently by the radical technic (but without a rib strut) with an incomplete correction of the deformity.

Best results have been obtained by the use of the radical technic in children from 2 to 6 yr. of age.

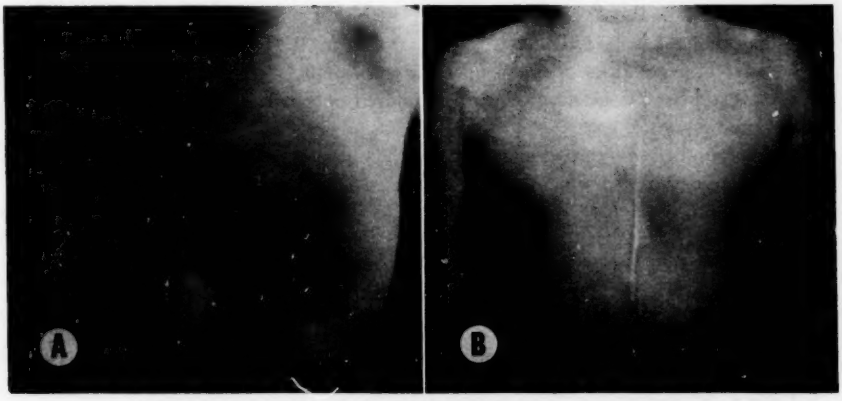

FIG. 2. Child operated on for funnel chest. A. Preoperative view at 2½ yr. of age. B. Postoperative view at 5½ yr. of age.

Within this age-range the operation is easy to perform because of the small size of the bones and cartilages. Postoperatively these children suffer very little pain or disability. As the patient grows older the operation becomes progressively more trying for him and more difficult for the surgeon. The author therefore feels that operation for funnel chest, when indicated, is best carried out between 2 and 6 yr. of age.

DISCUSSION

While very few children with funnel chest are disabled by the deformity, there is increasing evidence that a certain proportion of them will develop trouble as they grow older.

In addition to the possibility of cardiac or pulmonary disability, the psychologic hazards seem to be of equal or even greater importance. The author has found this so in questioning older patients. The preceding brief review of the literature shows that an appreciable number of adults with funnel chest were suffering from neurocirculatory asthenia. The author feels that such a condition might well be caused by a combination of the psychologic reaction to this deformity and by the "heart consciousness" caused by the heart beating within an unusually narrow space. In relation to the psychologic hazard, an excerpt from the questionnaire returned by Graham[18] follows: "It is only in the exceptional case that cardiovascular disturbances are produced which are severe enough to necessitate correction. I think that psychological reasons are sufficiently strong to justify

correction. I think that a child with considerable deformity would be most unusual if he could go through childhood with it without some permanent psychological scar."

Summary

Funnel chest as seen in childhood seldom produces disability.

A review of the literature reveals a growing number of cases of funnel chest in adult patients in whom varying degrees of cardiac disability have been described.

In a questionnaire answered by 25 American physicians, the majority feel that among adult patients with severe funnel chest there are some who suffer from cardiac or respiratory disability. There was a feeling that many of these patients undergo psychologic trauma.

Twenty-three of the 25 feel that operative correction of a severe degree of funnel chest should be undertaken in childhood.

A series of eight cases operated upon by the author is reviewed. Of these cases the outcome has been the most successful in children operated upon by radical surgery between 2 and 6 years of age.

The author believes that, for children with a severe grade of funnel chest, surgery should be recommended when they are between 2 and 6 years of age.

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Spanish Abstract

Tórax de Zapatero (Chonechondrosternon, Pecho en Embudo) Indicaciones Quirúrgicas y Tiempo de Realizar la Operación

La frecuencia del tórax de zapatero en niños y adultos obligó al autor a hacer una investigación que abarcaba dos puntos: Cómo se afecta el adulto que no se trata de pequeño su malformación, y

segundo, si debe operarse al niño con este padecimiento. El estudio se hizo a través de un cuestionario enviado a un grupo de médicos y cirujanos especializados en padecimientos de tórax, y de la observación de ocho niños que el mismo autor ha operado.

Resultados del cuestionario: Se solicitaron informes sobre si los pacientes adultos presentaban trastornos cardiacos, pulmonares ó psíquicos; si la malformación acorta la vida, y por último, si la operación debe realizarse en la infancia.

La mayoría de los médicos cree que los pacientes sí presentan diversos trastornos cardiacos y pulmonares, así como que un gran porcentaje de ellos sufren complejos psíquicos. No se logró uniformidad de opinión en cuanto al efecto de la malformación sobre la vida del enfermo, pero sí que el tratamiento quirúrgico debe realizarse tempranamente.

Casos quirúrgicos del autor: El tratamiento quirúrgico puede realizarse según la técnica de Brown de San Francisco, liberando la extremidad inferior del esternón de sus ligamentos posteriores; o bien según la de Garnier, liberando los cartílagos inferiores de sus ligamentos posteriores y realizando una osteotomía en la porción superior del esternón. De los casos del autor, dos se operaron con el primer procedimiento, sin mejoría (no encontró los ligamentos descritos por Brown en 7 de los 8 casos operados); de los otros 6 se tienen resultados muy favorables hasta la fecha, en particular en aquéllos operados entre 2 y 6 años de edad.

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OVARIAN MATURATION AND CYST FORMATION IN CHILDREN

By DONALD W. POLHEMUS, M.D.
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UNTIL recent years it was believed that ovarian follicle ripening began with puberty. However, a sufficient number of cases have been observed illustrating the presence of Graafian follicles very early in life to invalidate this opinion.[1-3] Cystic changes are also frequently seen in infancy, their etiology being rather obscure. It is the purpose of this report to summarize the ovarian changes commonly found in various age groups prior to puberty and to discuss the significance of these findings as they apply to current theories regarding histogenesis of the follicle cyst.

In the mature ovary a few follicles proceed through normal growth to ovulation, most undergoing atresia at some earlier stage. In the normal immature ovary ovulation does not occur, but several authors have pointed out that the follicles may reach various stages of development before undergoing atresia.[4,5] The process of atresia, which takes place rather rapidly, is characterized by degeneration of the ovum and granulosal cells, penetration of the basement membrane by connective tissue and blood vessels, collapse of the cavity and, finally, fibrosis. The earliest stage of atresia is termed the cystic stage. Occasionally a cyst, instead of continuing involution, will enlarge up to several centimeters in diameter with accumulation of a large amount of clear fluid. This constitutes a "follicle cyst," and several may be present simultaneously in the same ovary. Considerable confusion exists regarding classification of ovaries showing multiple follicle cysts and those with "small cystic degeneration." The latter term has been reserved by some authors for those ovaries which show an increase in connective tissue stroma with thickening of the capsule and diffuse formation of small follicle cysts throughout the parenchyma. Multiple follicle cysts are said to develop mainly in the ovarian cortex and to be unaccompanied by any marked fibrosis. Intermediate forms are the rule, however, and since these two conditions probably represent minor variants in the same basic pattern it is perhaps unnecessary to be overly concerned about confusing terminology.

MATERIAL

Ovaries from 171 female infants and children who have come to autopsy at the Los Angeles Children's Hospital during the last 5 yr. have been examined to provide material for this study (table 1). These ovaries were removed routinely whether or not macroscopic cysts were apparent. All the specimens have been carefully studied in regard both to maturation changes of the follicles and to the size and number of follicle cysts. These data were then correlated with the ages of the subjects and the disease processes leading to death.

FINDINGS

On viewing ovaries of infants and children the author has been impressed by the extensive evidence of follicle growth, which appears to proceed quite normally until

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TABLE 1

NUMBER OF PATIENTS IN AGE GROUPS

Age Group	No.
0–7 days	25
8–30 days	12
5–9 wk.	8
10–17 wk.	12
18–26 wk.	19
7–12 mo.	23
13–24 mo.	21
2–6 yr.	26
7–14 yr.	25
Total	171

atresia intervenes. Graafian follicles are usually present at birth, and by 4 months of age follicles measuring 1 to 2 mm. are frequently noted (Fig. 1). All stages of maturation and even cyst formation are often seen in the same ovary (Fig. 2). Scarring from recently degenerated follicles is common. Hemorrhage into a small cyst may rarely be seen. Small cysts, usually without a granulosal layer, measure from 2 to 7 mm. in diameter, and are regularly somewhat larger than accompanying intact follicles. Those follicles having an intact granulosal layer with or without an ovum seldom measure over 3.5 mm. in diameter.

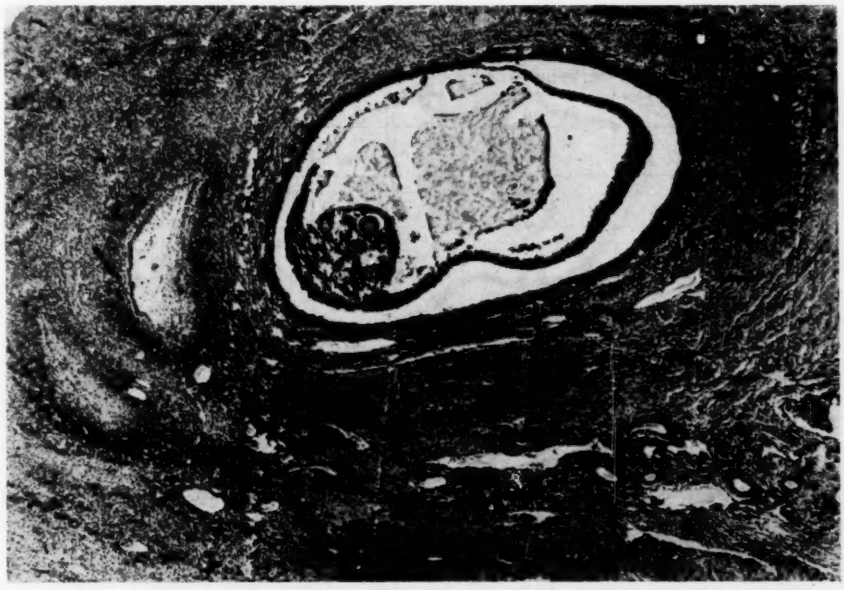

FIG. 1. Large Graafian follicle in ovary of 6½ yr. old child who died of chronic glomerulonephritis. Note atretic follicle on left. (×43)

FIG. 2. Ovary of 1 mo. old infant who died of duodenal atresia. Note variety of follicle changes. (×30)

Great variation in gross ovarian size is noted, this being mainly dependent upon the number and size of cysts. Noncystic ovaries follow their ordinary growth pattern.

Chart 1 lists the incidence of follicles of several sizes at various age levels. It is seen that there is a definite increase in follicle maturation as age progresses, with the most rapid changes taking place during the first four months. Cysts are here grouped with the Graafian follicles because of the impossibility of differentiating between early atretic follicles and true cysts.

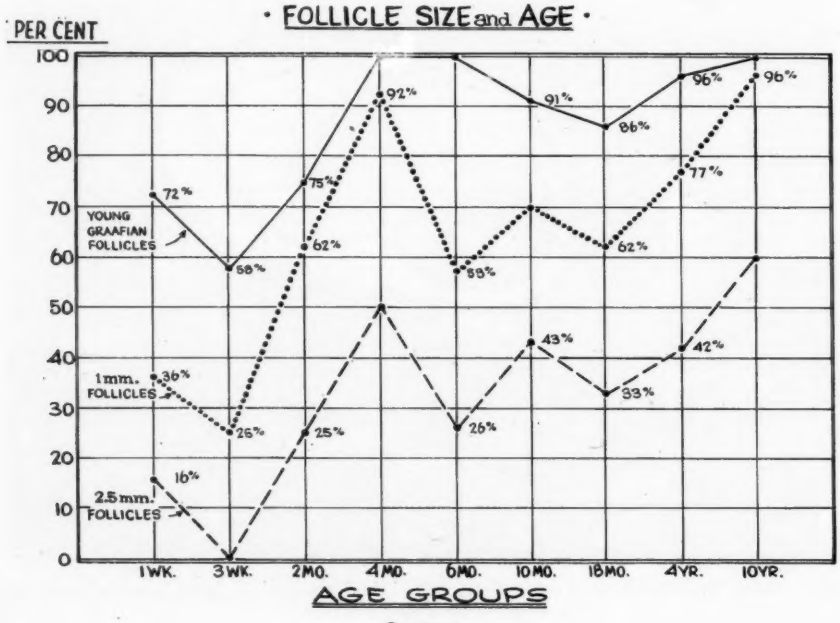

CHART 1

Polycystic ovaries are commonly seen at all ages and in this series attain a peak incidence at the fourth month. Most of the sections of cystic ovaries show from 2 to 5 grossly visible cysts, which occur both with and without a granulosal layer. Some of the ovaries involved seem to have a distinctly decreased number of follicles in their thinned cortex, but there is apparently no constant relationship between this and the extent of cystic change. Fibrosis of a significant degree is not seen other than locally where individual follicles have undergone atresia.

Chart 2 is intended to illustrate the incidence of extensive cystic changes at various ages. For purposes of comparison an ovary is classified as cystic if more than half of a midsaggital section is occupied by grossly visible cysts. It is realized that such a criterion does not necessarily reflect functional capacity.

Comparison of right and left sided ovaries reveals maturation changes of approximately the same extent in most cases. Polycystic changes are found to occur bilaterally somewhat more often than unilaterally.

An attempt was made to correlate the presence of follicles with the pathologic processes leading to death, but no unusual incidence of physiologic alterations of the ovaries was discovered in any particular disease group. Even in those children dying with hydrocephalus (a condition commonly believed to be associated with cystic ovaries[4]) there was no deviation from the changes seen in others of the same age group.

Discussion

Several basic facts regarding the extent of ovarian maturation and cyst formation in children now seem established. These can be correlated fairly well with some current theories of endocrine physiology.

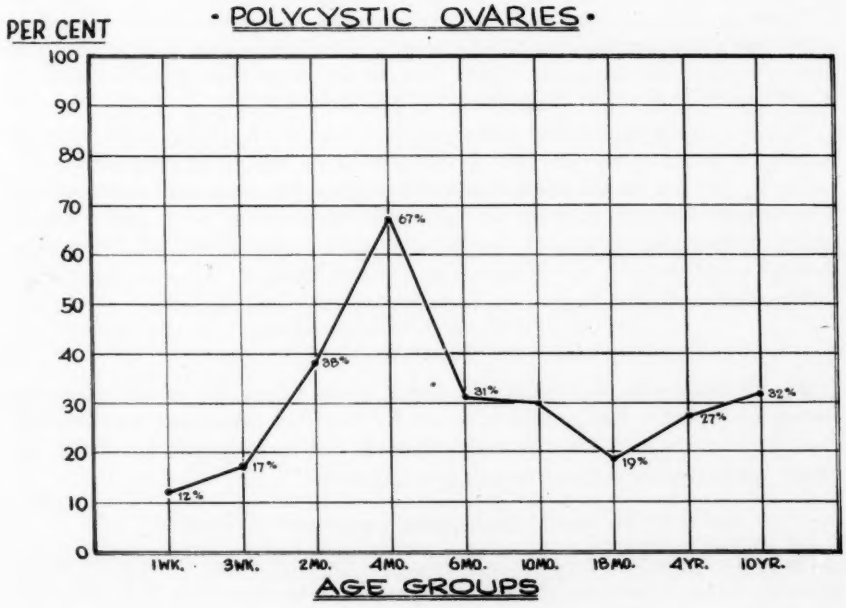

Chart 2

It is apparent that ovarian follicles commence maturation at or before birth, and follicles increase in size as the age of the child progresses. Pituitary gonadotropic hormonal stimulation would seem to be responsible, but this has by no means been confirmed in the laboratory. With the exception of the neonatal period when maternal hormones are carried over into the infant's blood stream, quantities of gonadotropic as well as estrogenic substances in the blood are believed to be extremely small.[6,7]

Polycystic ovaries are commonly found at all ages, but the greatest incidence in this series is at the fourth month. One would like to postulate that the carry-over of maternal hormones and their subsequent loss is in some way related. The actual cause of cyst formation in the ovary is, of course, uncertain, but most investigators agree that some endocrine imbalance is responsible. Recent theories have generally been concerned with a suspected derangement of gonadotropic hormone production,[8] and there is experimental evidence both in animals and humans that such a derangement can lead to cyst formation.[9-11]

The investigations of Reynolds, Delson and Lubin[12-17] indicate that straightening of segments of the normally spiralled ovarian arteries with local increase in hydrostatic pressure forces fluid into nearby follicles and creates cysts. Growth and development of arterial branches and their maintenance in a spiral shape are believed to be a result of estrogenic stimulation. Thus the greater frequency of cysts in later infancy as compared to the neonatal period[3] can be explained by the disappearance of the maternal estrogenic hormone from the infant's blood and consequent loss of the spiral configuration of the arteries. A small number of infants' ovaries have been examined[17] in regard to the shape of arteries adjoining cystic follicles, and the findings seem to bear out the above theory. Why there is so much variation in the extent of cyst formation and why so much cystic change is seen after infancy are questions not yet fully explained.

The author has found cysts or atretic follicles without a granulosal layer to be regularly larger than the largest Graafian follicles at all ages, indicating some fluid accumulation before regression of the atretic follicle. This finding seems quite consistent with the theory regarding segmental straightening of spiral arteries.

What becomes of all these cysts? Most regress spontaneously, although some may occasionally be precursors of large cysts and lead to serious mechanical complications.[18-20] Ruptured cysts and twisted ovarian pedicles have occurred during later childhood.[21-25] When large cysts retain their ova and granulosa cells they may be of clinical interest because of hormonal production,[4,26] several such instances having been noted in children showing sexual precocity.[27,28] It cannot be assumed, however, that cystic ovaries are etiologically significant in the great majority of sexually advanced children.

Summary

The results of study of a number of ovaries removed from infants and children at autopsy are presented. Follicle maturation and cyst formation were found to be extensive even in earliest infancy. The relationship of these findings to present knowledge and current theories regarding histogenesis of cysts is discussed.

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Associate Clinical Professor of Obstetrics and Gynecology, University of Southern California School of Medicine, Los Angeles.

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SPANISH ABSTRACT

Maduración Ovárica y Formación de Quistes en las Niñas

El concepto de que la maduración folicular se iniciaba con la pubertad, ha perdido terreno al encontrarse folículos de Graaf desde muy temprana edad; asímismo se han encontrado quistes. Este

trabajo presenta los cambios observados en los ovarios de 171 lactantes femeninos y niñas, estudiados a la autopsia en los últimos cinco años. Se observaron tanto desarrollo folicular como ovarios poliquísticos en todas las edades, preferentemente al cuarto mes. La maduración folicular se presentó en igual número en ambos ovarios y los cambios poliquísticos más a menudo bilateral que unilateralmente.

La maduración ovárica y la formación quística en niñas parecen relacionarse a la fisiopatología endócrina.

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STUDIES OF THE NATURAL HISTORY OF HERPES SIMPLEX INFECTIONS

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PRIMARY herpetic gingivostomatitis has come to be recognized as one of the common infectious diseases of childhood. The virus of herpes simplex was first implicated as the etiologic agent in 1938 by Dodd, Johnston and Buddingh.[1] Clinical observations incident to the etiologic studies led them to consider this disease as a primary infection occurring most frequently in children 1 to 3 years of age. Burnet and Williams[2] confirmed the fact that herpes virus could be readily isolated from the lesions and supplied the serologic evidence for the specific etiology and the primary nature of the disease.

Detailed descriptions of the specific herpetic etiology, the clinical manifestations and some of the epidemiologic characteristics of primary herpetic gingivostomatitis were subsequently presented by Scott, Steigman and Convey[3] and by Black.[4] These and the more recent studies of Anderson and Hamilton,[5] Blank et al.,[6] Ruchman and Dodd,[7] Dodd and Ruchman[8] and Rogers et al.[9] have established this disease as a well defined clinical and etiologic entity. The methods required for the isolation and identification of the virus and for demonstrating the serologic response to primary herpetic infection are now recognized laboratory procedures.[10, 11]

The collaboration in the original investigation[1] initiated a continued interest in this disease. The pediatric clinics and wards of Vanderbilt University Hospital provided cases for study during the course of several years. The virus of herpes simplex was isolated and identified and the specific serologic response to primary infection was demonstrated in 52 children ranging from 1 to 3 years of age. These cases provided the material required for the development of technics and methods. From them it was learned that herpes virus can be isolated from the stool during the active stage of the disease. It also became apparent that virus persisted in the mouth for considerable periods of time after recovery, a circumstance also noted in the reports of Scott, Steigman and Convey[3] and of Black.[4]

These experiences were preliminary to a more deliberately planned study. The outpatient clinics and contagious-disease wards of Charity Hospital of Louisiana provided the opportunity for a more comprehensive and elaborate investigation of the disease than had been previously possible. In the beginning the study was designed to ascertain the distribution of herpes virus in a series of patients during the course of the active disease. A determination of the character of the neutralizing antibody curve in the serum during the

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active disease, convalescence and for a considerable time thereafter was also planned. In the course of these investigations observations pertaining to the epidemiology of the disease were made. Consequently a considerable amount of epidemiologic data was collected. This report will present the results of these studies of the natural history of primary and recurrent infections.

Methods

Selection of Patients and Collection of Materials: Children with primary herpetic stomatitis were admitted from outpatient clinics to the contagious unit of Charity Hospital of Louisiana. Clinical course of each patient was studied in detail. Materials for virus isolation were obtained within 2 to 3 hr. after admission. These included mouth secretions, stool, spinal fluid and citrated blood. Blood was also drawn for serum studies. These materials were subsequently collected again at 4 or 5 day intervals during the period of hospitalization. Patients were discharged from hospital after 2 successive negative results had been obtained from each of the materials collected.

Specific therapeutic measures were not instituted. Frequent cleansing of mouth with sterile saline during the acute stage was the only measure applied.

Upon discharge from hospital the parents were requested to return patients for follow-up studies at monthly intervals. On these occasions mouth secretions and stools were collected for virus isolation. Blood for serum was drawn for continuation of serologic studies. Twelve patients were studied in this manner. Of these, 3 did not return. Remaining 9 returned at intervals of varying regularity for periods ranging from 1 to 10 mo. following onset of the disease.

Collection of Epidemiologic Data: The segment of population which depends on Charity Hospital of Louisiana served as a source for most of the epidemiologic data which were collected. Incidence of "healthy" or "normal" carriers of herpes virus was determined with mouth swabbings from individuals of various ages without evidence of herpetic infection who were available in the outpatient clinics. Survey on the incidence of neutralizing antibodies was made on serum specimens submitted to the Serology Laboratory for routine Kahn and Wassermann determinations. Studies on placental transmission of antibodies were performed on maternal and cord blood collected in the delivery rooms.

Virus Isolation: Chorioallantois of 12 day old chick embryos was used for isolation of herpes simplex virus from the materials collected. General procedure of inoculation by the "window" method and harvesting of membranal lesions for final identification of the virus is described in detail elsewhere.[12] Mouth secretions were collected by means of sterile swabs. Stool specimens were obtained as rectal swabs. Each of these materials was transported to the laboratory in tubes containing sterile saline 2 cc. To each cubic centimeter of these suspensions penicillin 500 u. and streptomycin 1 μg. were added immediately before inoculation. Citrated blood 5 cc. and spinal fluid 3 to 5 cc. were collected for inoculation. Entire amount of each of these specimens was divided equally in its distribution over the membranal surface of six 12 day embryos.

Inoculated embryos were examined after 48 and 72 hr. for development of characteristic membranal eruption produced by herpes simplex. Doubtful or equivocal lesions were harvested and subjected to at least 2 more passages in chorioallantois before being considered negative. Typical lesions were harvested and prepared for specific identification of virus.

Virus Identification: Typical membranal lesions produced by any of the materials were harvested, pooled, ground and made up into a 10% saline suspension by methods elsewhere described.[12] After centrifugation at 2000 rpm in the horizontal for 10 min. the supernatant served as virus suspension for specific neutralization by known antiserum prepared in rabbits with H.F. strain of herpes-simplex virus. Antiserum-virus mixtures and normal serum-virus controls were inoculated onto membranes of 12 to 14 day embryos. Specific neutralization was evident from inhibition or diminution of the pock count in membranes inoculated with antiserum-virus mixtures as compared with normal controls.

Serum Neutralization Tests: All sera were stored at 0° to 5° C. before testing. Fresh uninactivated normal and immune serum was found to possess marked nonspecific neutralizing capacity for herpes simplex. This property is heat labile and disappears completely during storage for 10 to 14 days at 0° to 5° C. Neutralizing antibody content was measured by the "pock counting" technic introduced by Burnet and Lush.[13] The H.F.-strain of herpes simplex was used as test virus.* Test inoculum was

* The H.F. strain of herpes simplex was kindly supplied by Dr. Peter K. Olitsky of the Rockefeller Institute.

prepared from a suspension of freshly harvested 48 hr. membranal lesions which was adjusted by dilution to produce 100 to 300 pocks with normal serum control inoculum. Patient's serum was tested in doubling dilutions from 1 : 0 through 1 : 512 against constant test inoculum. One cubic centimeter of each serum dilution was mixed with virus suspension 1 cc. and incubated at 37° C. for 2 hr. Chorioallantois of six 14 day old embryos was inoculated with 0.2 cc. of each serum-virus mixture evenly distributed by means of a tuberculin syringe fitted with a 27-gauge needle. Pock counts were made at 48 to 60 hr. following inoculation. Dilution which reduced the pock count to approximately 50% of normal control was arbitrarily chosen as the neutralizing titer of the serum.

Observations

The results obtained from the study of the 12 children with primary herpetic gingivostomatitis are presented graphically in charts 1 to 8. The acute phase of the infection lasted from 4 to 9 days with an average duration of 6 to 7 days. At this time the temperature returned to normal levels, the soreness of the mouth disappeared and regression of the lesions began. Convalescence during which the mouth lesions healed was completed

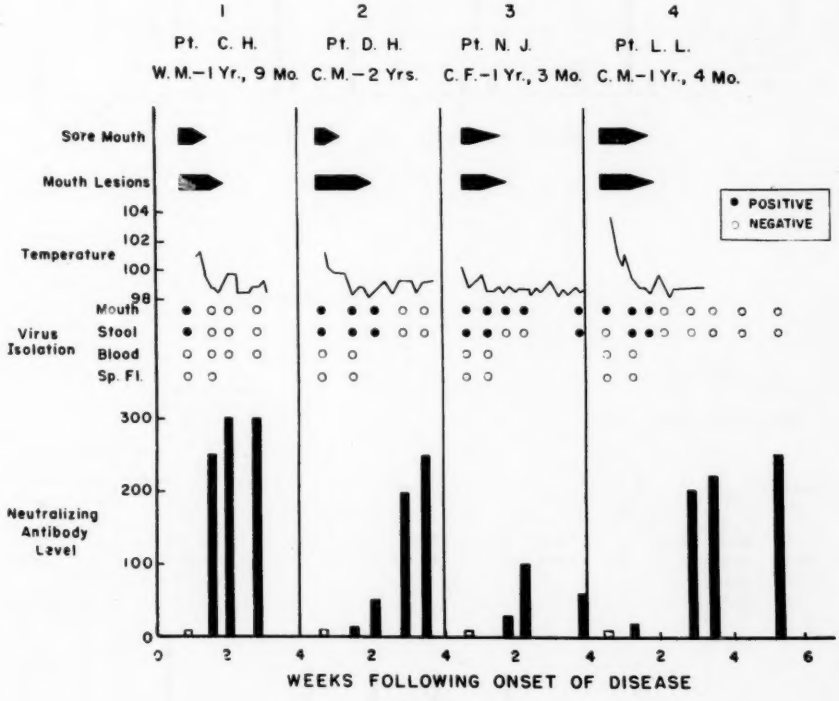

Chart 1

in different individuals by the twelfth to the eighteenth day following the onset of the disease. A more detailed consideration than this of the clinical manifestations will not be undertaken. The account which follows emphasizes addition to knowledge regarding this disease which these investigations have uncovered.

Distribution of Virus in Patients with Primary Herpetic Infection.—Saliva and stools:

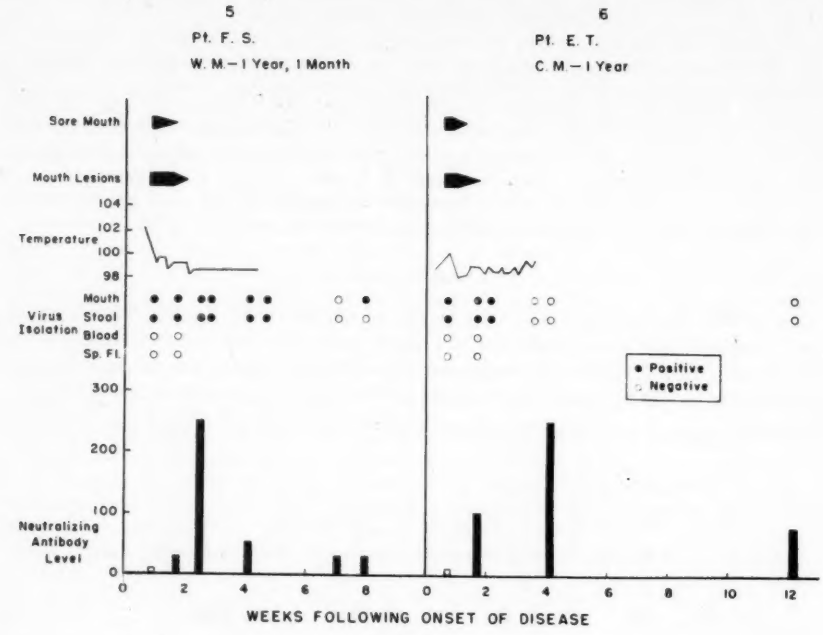

CHART 2

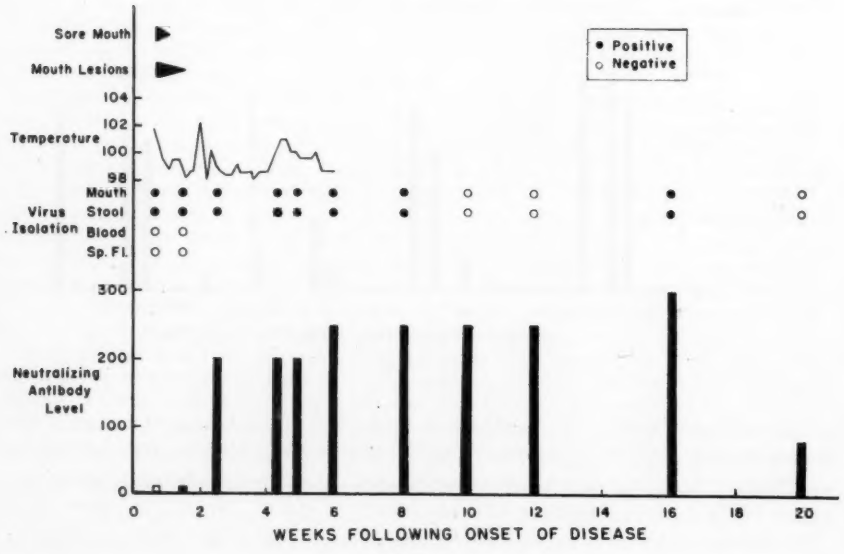

CHART 3

8
Pt. J. P.
C. M. – 2 Years

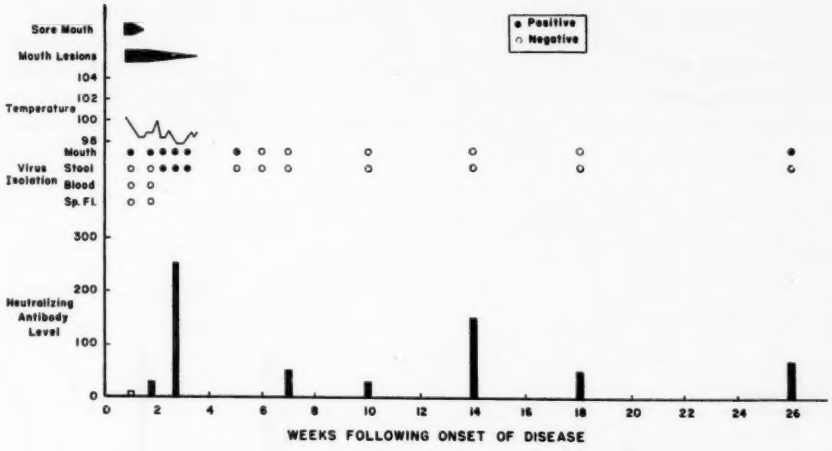

CHART 4

9
Pt. M. B.
C. F. – 2 Years

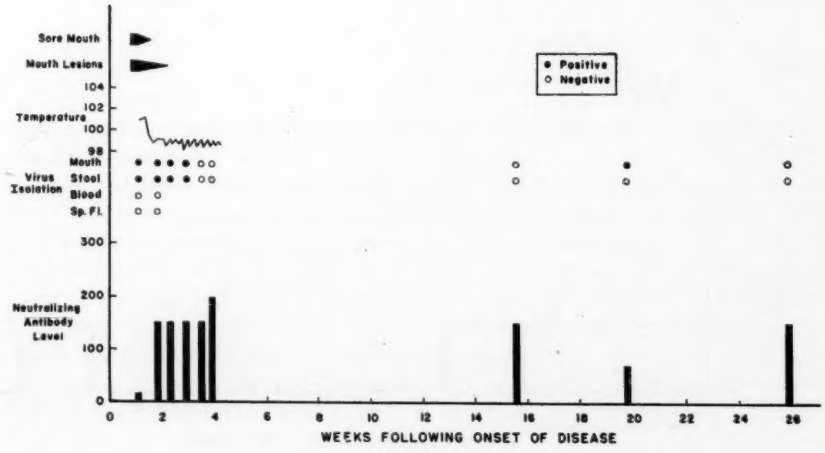

CHART 5

10

Pt. J. W.

W. F. — 2 Years, 9 Months

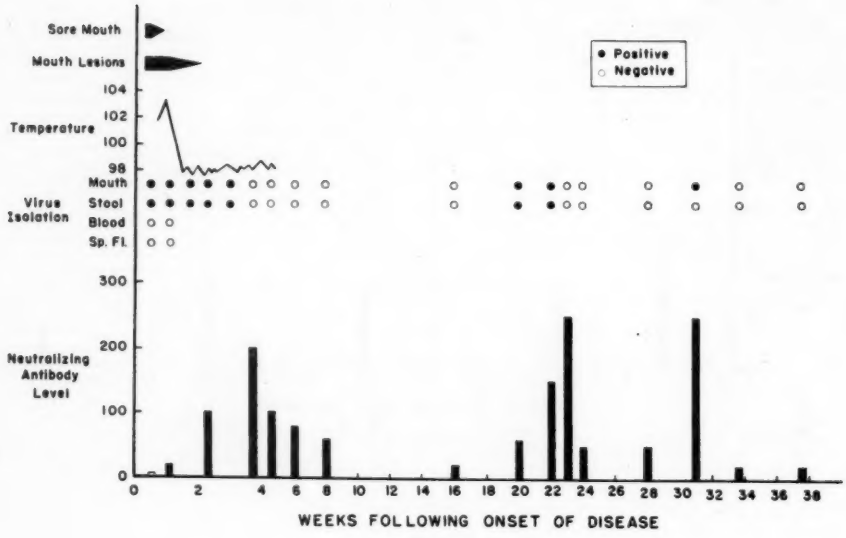

CHART 6

11

Pt. J. S.

W. F — 2 Years

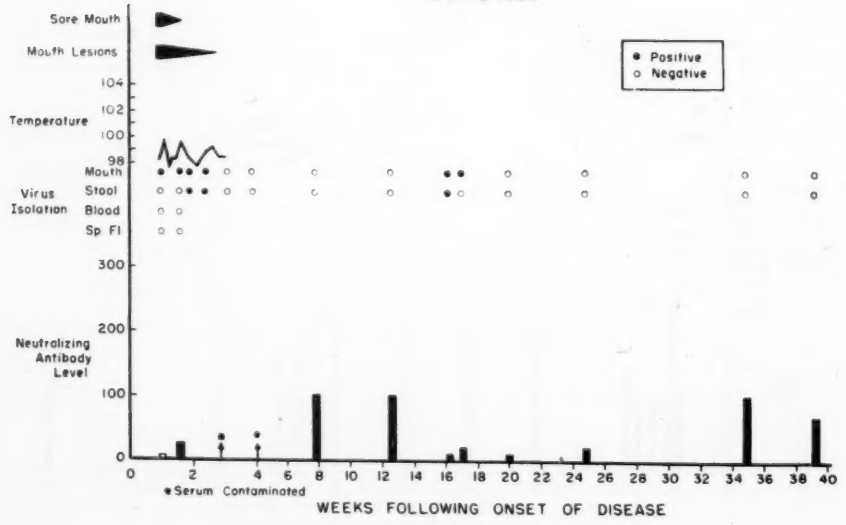

CHART 7

During the active stage of the infection herpes virus was readily isolated and identified from the mouth and rectal swabs obtained at repeated intervals in each of these individuals. Mouth swabs from four of the patients contained virus 3 to 4 days before it was isolated from the stools. It is assumed that most if not all of the virus appearing in the stools is derived from the oropharynx. There is a distinct probability that herpetic lesions may develop in the mucosa of the alimentary tract distal to the mouth and pharynx. Some children with primary gingivostomatitis have an accompanying tracheitis and bronchitis which may be herpetic in origin. These aspects of the problem require further investiga-

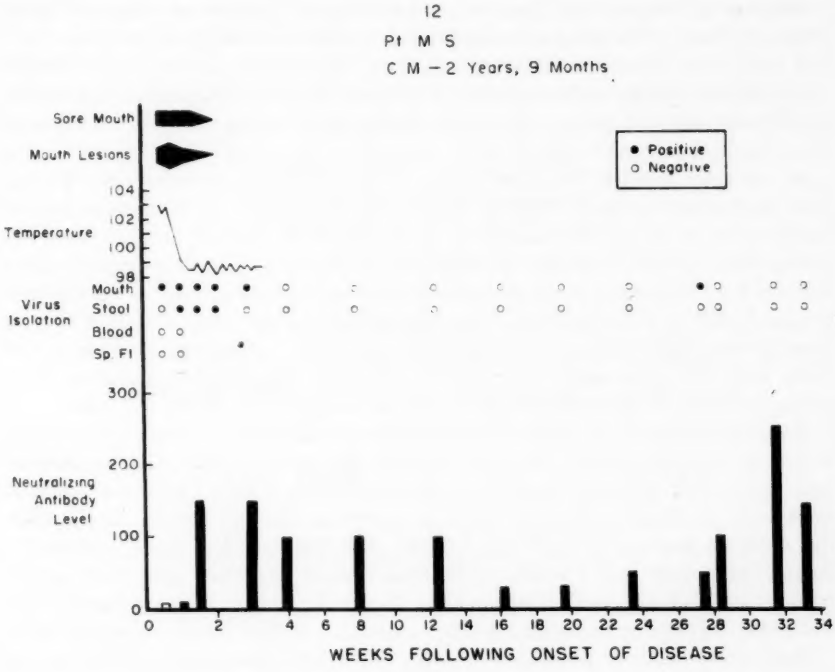

CHART 8

tion. Apparently virus is swallowed in large quantities so that its detection in the stool is readily accomplished.

Blood and Spinal Fluid: Virus was not isolated from the blood or spinal fluid obtained from any of the patients during the active stage of the disease. These results do not justify the conclusion that a viremia or entry of virus into the spinal fluid does not take place at any time during the disease or during the period of its incubation in the patient. None of these individuals was studied before the third day after the onset of the disease. This phase of the problem requires more investigation under circumstances where patients can be studied in earlier stages of the infectious process.

Time-period Following Onset During Which Virus was Recovered from the Saliva and Stools from Patients with Primary Herpetic Infection.—Considerable variety was noted

in the length of time following onset during which herpes virus could be isolated by inoculation of the chorioallantois with saliva and stool specimens from different patients. This ranged from 6 to 42 days. Virus could not be demonstrated in one individual beyond the sixth day at the end of the acute stage of the infection. The completion of convalescence in 4 of the remaining 11 marked the time after which virus could no longer be recovered. Virus was demonstrated in saliva and stools from seven individuals following complete recovery for periods ranging from 15 to 42 days following onset of the disease. The average number of days during which virus could be recovered from the patients in this series was 23 days.

Isolation of Herpes Virus from Individuals Without Evidence of Infection During Follow-up Studies After Recovery from the Primary Disease.—Reference to charts 1 to 8 will indicate the number of follow-up studies and the intervals at which they were made in 9 of the 12 patients of this series. After discharge from the hospital a varying number of weeks elapsed with different individuals during which herpes virus was not recovered from the saliva and stool collected on the occasion of the return visits. Herpes virus was again recovered from the saliva and stools or saliva only obtained from seven of these individuals after the intervals during which its presence could not be demonstrated. It was possible to collect saliva and stools from two of the children at weekly intervals during these episodes. From one of them, Patient 10, virus was isolated from the saliva and stool on two more successive weekly occasions. From the other the saliva only produced herpetic infection of the chorioallantois after a one week interval. Following these episodes virus could not be isolated from each of the children on subsequent return visits. Virus was again isolated from the saliva only from Patient 10 after an interval of 12 weeks following the first episode when virus was isolated from mouth and stools.

No clinical evidence of herpetic infection could be ascertained in each of the children at any of the return visits. These observations thus indicate that following recovery from the primary infection herpes virus can be recovered from the saliva and stools at times when no clinical evidence of infection is present. The time interval during which this condition may persist cannot be definitely stated. It is evident that it may have a duration of at least 1 or 2 weeks. Under these circumstances these individuals may be regarded as "healthy carriers" of herpes virus. They presumably may serve as sources from which the virus can be transmitted to other individuals in their immediate environment.

Neutralizing Antibody Response to Primary Herpetic Gingivostomatitis.—Charts 1 to 8 present graphically the results obtained from measuring the neutralizing antibody response in the serum of 12 children with herpetic stomatitis. Neutralizing antibodies were first detected from the fourth to the seventh day following onset. They increased rapidly thereafter, reaching maximum levels during the second or the early part of the third week. Considerable variation in the rate of production and eventual maximum antibody level was noted. The maximum level was maintained in the majority of cases for 3 to 4 weeks following onset of the disease. In Case 7 it was maintained for 16 weeks. It might be concluded that the continued presence of virus in the mouth and stools of this individual for at least 8 weeks was responsible for maintaining a high level of antibody for this period. In Case 5, however, the antibody level dropped during the time when virus could still be recovered from mouth and stools.

In all instances where follow-up studies were made it was demonstrated that the maximum antibody level which developed was not maintained indefinitely. The neutralizing

antibody titer of the serum subsequently dropped to lower levels. These observations confirm those made recently by Gajdusek, Robbins and Robbins[11] who followed the complement fixing titer of the serum in a series of patients with primary herpetic infection.

Subsequent significant increases in neutralizing antibody levels were noted especially in Case 10 on two occasions. In each instance the increase in antibody developed during an episode when virus was recovered from the patient and no evidence of infection was discernible. Following each rise the antibody level dropped quite promptly. These instances might be considered to represent inapparent infections. Case 11, however, illustrates that the antibody level does not necessarily increase under these circumstances. The factors which determine whether an increase in antibody level will be stimulated during episodes when virus can be recovered without evidences of infection are not evident from these studies.

Recovery of Herpes Simplex Virus from the Mouths of "Normal" Individuals.—The recovery of virus from the saliva of children at times when they presented no evidence

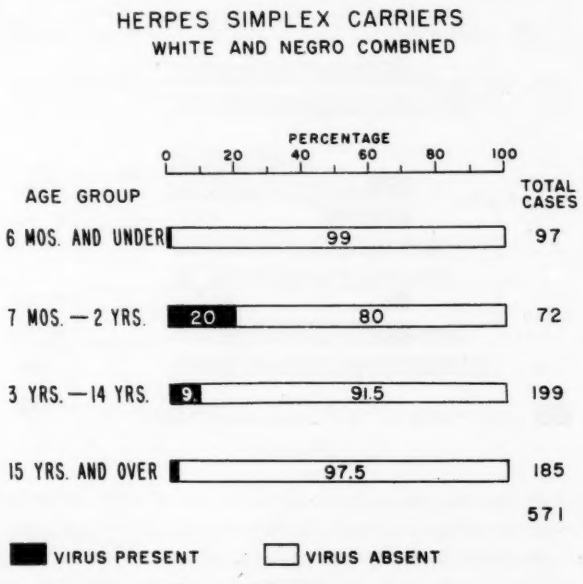

CHART 9

of herpetic infection prompted a more extensive survey of the occurrence of this circumstance. Mouth swabbings were collected from 10 to 30 individuals at a time. Each specimen was tested for its capacity to produce herpetic infection in the chorioallantois of 12 day chick embryos. This procedure was continued at weekly or twice weekly intervals over a period of several months. Mouth swabs from a total of 571 individuals selected at random were tested in this manner. The combined results are presented graphically in chart 9.

Herpes virus was recovered from the saliva of 15 or 20% of 72 children in the 7 month through 2 years age group. The saliva of 18 or 9% of the 199 children in the

3 through 14 years age group produced herpetic infection of the chorioallantois. In 185 individuals 15 years and over only 5 or 2.4% were encountered from whose saliva herpes virus could be recovered. Under 6 months of age this circumstance occurs rarely, having been noted in only one 3 month old Negro infant out of a group of 97 white and Negro infants combined. A total of 39, or approximately 7%, isolations of herpes was made from the entire group of 571 individuals.

This group included 386 children, 187 of whom were white and 199 were Negro. A comparison of the frequency with which herpes virus was recovered from the saliva of white children and of Negro children is presented graphically in chart 10.

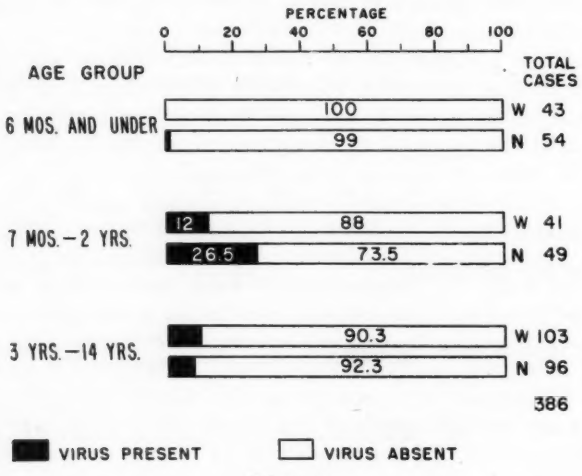

CHART 10

Herpes simplex virus was recovered from the mouth of 12% of white children and from 26.5% of Negro children in the 7 months through 2 year age group. No striking difference was encountered in the 3 to 14 year age group.

Of the 39 positive isolations, 33 or 85% were made from children under 15 years of age. Herpes virus was recovered with greatest frequency in the saliva of normal children in the 7 month through 2 years age group. Conditions favorable to this circumstance seems to exist more commonly among Negro than white children of this age. Environmental factors and hygienic standards perhaps account for much of this striking difference. A comparison of white children in the 7 months through 2 years age group and the 3 through 14 years age group presents no marked difference. Children thus appear to harbor herpes virus with sufficient frequency to constitute a considerable reservoir from which this agent may be disseminated.

Herpes Simplex Neutralizing Antibodies in the Serum of Individuals in Different Age Groups.—Undiluted serum samples from 591 individuals were tested for the presence or absence of herpes neutralizing antibodies by means of the "pock counting" technic on

the chorioallantois. The total included serum from 242 white and 349 Negro individuals. A comparison of the results of this survey of this segment of the white and the Negro population is presented graphically in chart 11.

The serum of 79% of white and 93% of Negro infants 6 months of age and under contained herpes neutralizing antibodies. It will subsequently be demonstrated that this may be accounted for by passive transfer of the antibodies from the mother during pregnancy. The 7 months through 2 years age group contains the greatest percentage in which no antibodies could be demonstrated. This is the group in which most of the cases of primary herpetic gingivostomatitis occur.[6] Immunity as reflected by the presence of

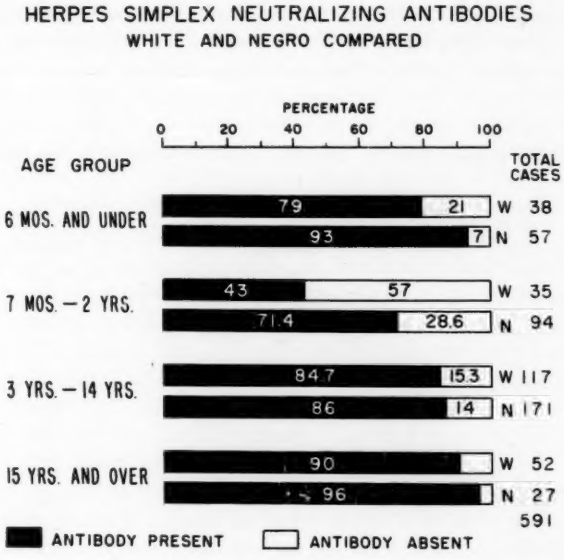

CHART 11

neutralizing antibodies in the serum of children in this group presumably becomes actively established in many instances as the result of a primary infection. The occurrence of inapparent infections which may stimulate an active immunity must be considered. The present studies, however, permit of no conclusions regarding the frequency with which active immunity is stimulated by inapparent infection.

Neutralizing antibodies were found to be present in the serum of 43% of the white and 71.4% of the Negro children in the 7 months through 2 years age group. Opportunities for contact and infection with herpes virus apparently occur with much greater frequency among Negro than among white children of this age. This is suggested by the observation that in this age group herpes virus was recovered from the saliva of 26.5% of the Negro and from 12% of the white children.

In the 3 through 14 year age group 84.7% of the white and 86% of the Negro children had neutralizing antibodies in the serum. During this period of life neutralizing antibodies develop in a considerable proportion of white children. The school rather than the home environment seems to afford white children greater chances of contact with

or infection by the virus. The greatest proportion of Negro children presumably come into contact with herpes at home and are more likely to develop antibodies at an earlier age.

The serum of 90% of the white and 96% of the Negro individuals 15 years and over contained neutralizing antibodies to herpes. The number of serum samples tested in this group is too small to allow conclusions regarding the significance of the difference observed. However, 14% more Negro than white infants 6 months of age and under appear to have acquired antibodies by passive transfer. This would seem to indicate that neutralizing antibodies are present in the serum of a higher percentage of Negro than white individuals.

Placental Transmission of Herpes Neutralizing Antibodies.—Blood for serum was drawn from mothers immediately prior to delivery. Placental blood was collected from the cord at the time of delivery. The neutralizing antibody titer was measured at the

TABLE 1

PLACENTAL TRANSMISSION OF HERPES SIMPLEX NEUTRALIZING ANTIBODIES

Serum Pair No.	Neutralizing Antibody Level	
	Maternal	Placental
1	128	128
2	32	64
3	64	64
4	0	0
5	512	512
6	256	128
7	512	256
8	128	128
9	512	512
10	1024	1024
11	256	256
12	512	512
13	512	512

same time on each pair of serums by the "pock counting" technic as described. Thirteen pairs of maternal and placental blood were tested for neutralizing antibody levels in this manner. The results obtained are presented in table 1.

These results indicate that neutralizing antibodies to herpes simplex traverse the placental barrier. Approximately the same antibody level present in the maternal circulation becomes established in the placental circulation. When antibody is not detectable in the maternal serum, it cannot be detected in the placental serum. Recently Kempe, Benenson and Jackson[14] have demonstrated that similar circumstances obtain in the placental transmission of antibody to vaccinia virus.

DISCUSSION

The virus of herpes simplex has been regarded as a highly successful parasite.[15] Certain patterns in host-parasite relationship have become established which assure the perpetuation

of the parasite population without profoundly disturbing the host population. Some of the features which characterize these patterns have perhaps become more evident in these studies. It is apparent that a reservoir of considerable magnitude is maintained from which the infectious agent is constantly disseminated. Individuals with primary herpetic infection provide a rich source of virus for considerable periods of time. Children, in the younger age groups especially, constitute temporary "normal" carriers at frequent intervals. Cases of recurrent herpetic infection are additional sources from which the virus is spread.

Saliva and feces appear to be the chief vehicles of transmission. Environments in which low hygienic standards and crowding prevail provide the best opportunities for a more efficient dissemination of the virus. Under these circumstances the majority of the host population becomes actively immune either by developing the primary type or from inapparent infections. This natural process is delayed where improved hygiene and absence of crowding interfere with the transmission of the virus. Burnet[15] has emphasized the fact that herpetic stomatitis is encountered with greatest frequency in children of the lower income groups. The present studies provide an additional explanation for this occurrence.

It has been postulated that the persistence in a latent state is one of the mechanisms which serve to maintain herpes virus in its human host.[15, 16] Recurrent herpetic infections are considered in most instances to represent recrudescence of endogenously established virus. The present investigations have not provided much information which would contribute to a solution of the problem of latent herpetic infection. It is evident from the limited observations made that if herpes virus becomes established in a latent state following primary infection it does not serve as a stimulus for maintaining a persistently high level of neutralizing antibodies. The demonstration that herpes virus can be recovered from a reservoir of considerable magnitude increases the probability that exogenous infection may account for many instances of recurrent herpes.

Placental transmission has been demonstrated to establish passive serologic immunity in the newborn infant. Passively acquired antibodies appear to be an important factor in providing protection against primary infection during the first 6 to 12 months of life. The incidence of passive immunity in the infant population develops in direct proportion to the incidence of actively acquired immunity in the adult population. It remains to be determined whether inapparent infections capable of stimulating active immunity may become established in infants in whom passively acquired antibodies have reached a low level. Such a demonstration could explain the general impression that many children escape the primary infection in overt or manifest form and nevertheless have acquired active immunity. Anderson and Hamilton[5] have presented good serologic evidence for the frequent occurrence of inapparent infection in children in the susceptible age group.

Considerable individual quantitative variation in the serologic immune response to primary herpetic infection was observed in these studies. An "all or none" response described by Burnet[15] could not be demonstrated. Maximum antibody titers are usually attained during the second or third week following the onset of the disease. Following this the titer drops to low levels after which more or less fluctuation is observed. The data presented by Dodd and Ruchman[8] shows marked variation in herpes neutralizing antibodies in serum from different individuals. Jawetz[17] has also made the same observations.

Investigations of this type will have to be continued in order to obtain a more comprehensive understanding of the natural history of herpes simplex infections in man. The present studies have provided some insight into certain phases of this problem. Further elucidation of the nature of "successful parasitism" may reveal principles which are applicable in establishing more effective control of other viral infections of man.

Conclusions

In a detailed study of 12 individuals with primary herpetic stomatitis the virus was recovered from the mouth and stools during the acute stage, convalescence, and for varying periods of time thereafter. The average time period during which virus could be recovered from these sources was 23 days after the onset of the disease. Virus could not be recovered from the blood or spinal fluid, but patients were not available for study before the third day of the disease.

Neutralizing antibodies to herpes simplex were first demonstrated in the serum from the fourth to seventh day of the disease. The antibodies attained a maximum level during the second or third week. Considerable differences in individual antibody levels were noted. The maximum antibody concentration was not maintained and dropped to relatively low levels over varying periods of time in each patient studied.

Herpes simplex virus was recovered from the mouths of many individuals presenting no clinical evidence of herpetic infection. The virus was recovered from 7% of 571 normal individuals of various ages. It was recovered from 1 infant out of 97 under 6 months of age, from 20% of 72 children of 7 months to 2 years, from 9% of 199 children 3 to 14 years of age and from 2.5% of the 185 adults. The incidence of normal carriers was found to be highest (26%) in Negro children in the 7 months to 2 year age group.

Neutralizing antibodies were demonstrated in the serum of 43% of white and 71.4% of Negro children in the 7 month to 2 year age group. The serum of 84.7% of white and 86% of Negro children in the 3 to 14 year age group contained antibodies to herpes. In adults 90% of white and 96% of Negro individuals had antibodies to herpes in the serum. Natural active immunity appears to be established at an earlier age in the segments of the population in which the highest carrier rate was demonstrated.

Neutralizing antibodies were demonstrated in the serum of 76% of white infants and in 90% of Negro infants 6 months of age and under. The placental transmission of neutralizing antibodies was demonstrated. Approximately the same level of antibody was found to be present in the maternal serum and in the serum obtained from the placenta.

Acknowledgments

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SPANISH ABSTRACT

Estudios sobre la Historia Natural de las Infecciones por Herpes Simplex

Los autores estudiaron detalladamente 12 niños con estomatitis herpética primaria y numerosos niños, adultos, y madres normales habiendo llegado a las siguientes conclusiones: 1° Se aisló el virus del herpes simplex de la boca y evacuaciones de niños con estomatitis herpética durante el estadío agudo, la convalescencia y en periodos variables después de ésta. El promedio del periodo de tiempo durante el cual el virus pudo ser aislado de dichas fuentes fué de 23 días después del principio de la enfermedad. El virus no pudo ser aislado de la sangre o líquido cefalorraquídeo después del tercer día de enfermedad. No se pudieron obtener pacientes para estudiar este aspecto antes del tercer día del padecimiento. 2° Los anticuerpos neutralizantes para el herpes simplex se demostraron primero en el suero, entre el cuarto y séptimo día de enfermedad, alcanzando su nivel máximo entre la segunda y tercera semana. Se apreciaron diferencias considerables en los niveles individuales de anticuerpos. No se mantuvo la concentración máxima de anticuerpos, sino que cayó a niveles relativamente bajos en periodos variables de tiempo en cada paciente estudiado. 3° Se aisló el virus del herpes simplex de las bocas de muchos individuos que no presentaban evidencia alguna de infección herpética. Efectivamente, se encontró en el 7% de 571 individuos normales de distintas edades. Se aisló en un lactante fuera de 97 de menos de 6 meses, en el 20% de 72 niños de 7 meses a 2 años, en el 9% de 199 niños de 3 a 14 años de edad y en el 2.5% de 185 adultos.

La incidencia más alta de portadores normales (26%) se encontró en niños de raza negra en el grupo de 7 meses a 2 años de edad. 4° Se demostraron anticuerpos neutralizantes en el suero del 43% de niños blancos y 71.4% de niños negros del grupo de 7 meses a 2 años de edad y en el 84.7% del suero de niños blancos y 86% de niños negros en el grupo de 3 a 14 años de edad. En los adultos se demostraron anticuerpos en el suero sanguíneo del 90% de individuos blancos y en el 96% de individuos negros. La inmunidad natural activa parece establecerse en edad más temprana en las capas de población cuyos índices de portadores se demostró ser el más alto. 5° Se demostraron anticuerpos neutralizantes en el suero del 76% de lactantes blancos y en el 90% de lactantes negros, ambos de 6 meses de edad o menos. Se pudo demostrar la transmisión placentaria de anticuerpos neutralizantes. En el suero sanguíneo materno se encontró aproximadamente el mismo nivel de anticuerpos que en el suero obtenido de la placenta.

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TREATMENT OF ENTEROBIASIS (PINWORM INFESTATION) WITH DIPHENAN®, EGRESSIN® AND GENTIAN VIOLET

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THERE is at present no recognized satisfactory treatment for enterobiasis. Gentian violet usually produces a cure but due to reinfestation freedom from symptoms may be short-lived. Repeated treatment with gentian violet is sometimes avoided because of the gastric upsets produced and the necessity for the patient—usually a child—to swallow the enteric-coated tablets whole. Hygienic programs may be helpful in preventing reinfestation, but they are too burdensome to be endured for long periods.

Among the numerous drugs which have been offered as overcoming the above objections, two are of special interest. The first, p-benzylphenyl carbamate, though coming into prominence only since 1948 was developed as butolan®* in Germany in 1920. Experimental and clinical observations were reported on its efficacy and lack of toxicity.[1, 2] Inasmuch as various supportive expedients were included in the clinical trials, the drug as an isolated factor could not be evaluated. In recent years, under the name diphenan® this drug has been used extensively in England[3] and the United States,[4] although critical studies of its efficacy in the treatment of enterobiasis still have not been reported.

The other drug, 3-methyl-6-isopropylphenyl ester of N-isoamylcarbamic acid (egressin®†), was first reported in 1949.[5] It was found to be nontoxic and effective in studies carried out in Europe.[6-8] In more recent studies, however, egressin® has been found to be of doubtful value in the treatment of enterobiasis.[9, 10]

The present study is a comparative clinical evaluation of diphenan®, egressin® and gentian violet.‡

METHODS AND MATERIALS

Most of the studies were conducted on 47 girls, 3 to 15 yr. of age, in an asylum. Others were carried out on children who were hospital ward and clinic patients.

Technic of diagnosis was a previously described modification of adhesive-cellulose-tape method.[11] Perianal impressions were taken by parents of outpatients. For all others, one individual took impressions and did microscopic examination of preparations. As many examinations as feasible were made, and individuals with less than 3 recent pre- and 5 post-treatment tests were excluded from analysis.

Patients were treated with one or more of the 3 drugs. Combinations were not used, but in case of failures patients were retreated with the same or another drug. Egressin® was given orally in the amount of 0.1 gm./kg./day in 2 or 3 divided doses for 5 days without purgatives. This is

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* F. Bayer and Company, Elberfeld-Leverkusen.

† E. Merck, Darmstadt, Germany.

‡ Diphenan® and egressin® were supplied by Burroughs-Wellcome and Sharp & Dohme, Inc., respectively. Two brands of gentian violet medicinal in 4 hour enteric-coated tablets were used—Seal-Ins (Seal-Ins Laboratories, Los Angeles) and Enseals (Lilly).

essentially the same schedule as was used by Askue.[10] For children 2 to 12 yr. old, earlier investigators used up to 1 gm. 3 times daily for 2 days, followed by purgation on 3rd day. The dosage of diphenan® was in all cases at least equal to, and usually 2 to 3 times, the standard daily dose and was given for periods of 6 to 29 days. All the 46 institutionalized children who received this drug took 0.5 gm. 3 times a day for 6 or 7 days. Since it was possible that the several earlier favorable reports on diphenan® could be attributed entirely to the simultaneous program of hygienic measures and enemas, such a program was omitted from the regime of these patients. Gentian violet was given orally in 2 or 3 doses daily, 2 hr. after meals, for 7 days. Total daily dose, governed somewhat by tablet-sizes (3/20 gr. = 10 mg. and ½ gr. = 32 mg.), was approximately 10 mg./yr. of apparent age.

A control group of 24 patients was tested in the same manner as the others for various periods of time, but received no treatment.

Because the subjects could not be followed throughout the period of probable prepatency of infestation and instances of spontaneous natural loss of infection could not be recognized with certainty, there could be no absolutely reliable single criterion of cure in the individual case. Arbitrarily, those who became negative on the 2nd or 3rd day after completion of treatment and remained so through at least 4 test days within the following week were regarded as cured. It is recognized, however, that some of these individuals possibly would have become negative without treatment.

Results

Egressin®: Sixteen institutionalized girls were given a five day course of egressin® (Part II of chart 1). All of them had been positive at least 4 times within the preceding nine day period. One patient gave no positive tests during the eight day period after treatment, the rate of possible cure being 6%. The frequency of positive tests was reduced from 86% before to 54% after treatment. Treatment with diphenan® was begun after the eight day follow-up period. A tape from the single cured patient was positive 13 days after treatment with egressin®. No symptoms of toxicity were noted.

Diphenan®: Forty-six institutionalized girls were treated with diphenan® (Part I, chart 1) including all 16 of those who completed treatment with egressin® eight days previously. Of five who were repeatedly tested with negative results before treatment, three became positive within one week afterwards. Among those with pretreatment positive tapes only 15% could be regarded as possibly cured. For the group as a whole, the difference between the frequency of positive tests before and after treatment was negligible. Seven additional patients were treated with diphenan® for periods of up to 29 days. One became negative on the last day of an eight day course and remained negative for two weeks. All others were repeatedly positive after treatment and one patient who was treated for 29 consecutive days remained positive daily throughout the period and for 10 additional days. There were no evidences of toxicity.

Gentian violet: Twenty-seven children were treated for seven days with gentian violet (Part III, chart 1). All had at least two positives out of the four daily tests preceding treatment. Most of this group were failures from previous treatments with egressin® and diphenan® and had records of being almost continuously positive for periods of more than two weeks. Beginning on the second day after treatment, 20 were continuously negative. Three of the seven others had four successive negative tests when the study was ended and were perhaps actual cures. Of 103 pretreatment tests 94% were positive while only 11% of 156 were positive after treatment. Nausea, vomiting or cramps occurred in two patients only. In addition, six outpatients were treated successfully with gentian violet in the same manner. Two of these were followed long enough to observe the return

CHART 1. Results of testing for pinworm infestation. Each line represents records on individual patient, treatment periods being designated by underscoring. Results of successive days' tests are shown as follows: positive, +; negative, —; no test, blank.

of positive tests after a lapse of 37 and 44 days. As defined, the cure rate for all patients treated with gentian violet was 80%.

Untreated: Untreated ward and outpatients, most of whom were in close contact with infested children, were followed for various periods. Infestation was found in 24 of them (Part IV, chart 1). The chief point of interest to be observed in this group is that if a seven day course of treatment with a wholly ineffective drug had been instituted immediately after the first positive test had been obtained, apparent cures (on the basis of the above described criteria) would have resulted in nine instances. Cures based on one random post-treatment test would have occurred in over 50% of the subjects and on the basis of two random tests, cures would have occurred in about 25%. However, since positive and negative results tend to run in series rather than by random distribution, 2, 3 or 4 consecutive days of testing still would have resulted in a considerable number of apparent

cures. For example, while two random tests would have given, on the average, a 25% cure rate, two consecutive daily tests would have given, by chance, a cure rate of approximately 40%.

The results from the untreated group were strikingly like those with diphenan®, in which the rate of cure, or remission, was 55% among those with one pretreatment positive, 29% among those with two, and 4% among those with three or more pretreatment positives. Thus no effect of diphenan® on pinworm infestation was demonstrated. Such cures as were obtained can more logically be attributed to natural causes. When four patients were treated by means of nightly enemas, all were consistently negative during the seven day treatment period, but positive tests resumed soon thereafter. The difference in cure rate between the egressin® and untreated groups was of no significance. The cure rate in the gentian violet group was highly significant as compared with all other groups. It appeared that diphenan® was useless and any value in egressin® was highly improbable, while the seven day course of gentian violet was unquestionably effective.

Discussion

Both the clinical and laboratory diagnosis of enterobiasis are based directly or indirectly on the exit of the causative organism from the body. This peculiarity of the infestation is one of the pitfalls of investigation into its therapeusis, since the recent presence of either symptoms or of pinworm eggs in the perianal area does not necessarily prove current infection. Hall and Cram[12] have pointed out that a positive anal swab possibly may be the result of the desertion of the host by the last infesting pinworm. While Sawitz and Karpinos[13] have provided some idea of the significance of the negative test for pinworm infestation and the necessity for repeated tests for presumptive cure, it is no less necessary to obtain repeated positive tests in order to assume that the infestation is present and likely to continue even to the time when treatment is started. Those individuals whose tests are positive daily are most likely to produce positive tests again during a test period 1 or 2 weeks later, and those with but one positive test out of a series of daily tests are very likely to have groups of daily negative tests after treatment, separated by an occasional positive one. Brief periods of testing these latter patients may easily lead to false interpretations.

These principles are illustrated by the observation that spontaneous "cure" occurred in inverse proportion to the frequency of positive tapes during the first week of study. While these ideas must seem self-evident, they have rarely been applied in the testing of a drug's effect upon pinworm infestation. Favorable reports of pinworm remedies based on treatment of cases with a single-test diagnosis are thus to be regarded with suspicion.

The rate of cure with gentian violet therapy in the present study was somewhat lower than was expected on the basis of the writers' earlier observations. On the other hand, the incidence of nausea and vomiting was rather low. Possibly in some instances the enteric-coated tablets failed to break down in the bowel. Previously, the tablets from certain lots frequently have been recovered intact from the stools. If properly released, gentian violet produces a uniform violet discoloration of the feces. On the other hand, the untimely disintegration of fractured or otherwise imperfectly coated tablets may account for occasional nausea and vomiting. Because of these possible obstructions to successful treatment, it is worth while to have patients observe the stools and report if they are not uniformly purplish throughout the period of treatment.

A point of interest which may bear on the mechanism of the action of gentian violet is the continuation of egg-deposition at the anus for a few days following treatment. Patients with positive tapes 1 or 2 days after cessation of treatment apparently should be considered as cured provided there are no subsequent positives. In this study a few patients became negative as late as the fourth day after treatment. While such instances were not interpreted as cures, previous experience has indicated that testing of the patient as a check on the success of treatment may logically be delayed to at least the fourth day and continued for whatever period is feasible.[14, 15] It was for that reason that the periods of treatment and testing both were extended beyond reasonable limits on selected cases in this study.

Summary and Conclusions

Pinworm infestations in children were diagnosed and followed for various periods by means of the cellulose-adhesive-tape technic, after which they were treated with diphenan®, egressin® or gentian violet and again followed for six days or longer. Twenty-four children were likewise tested but not treated.

Diphenan® was found to have no detectable anthelmintic effect when given in high dosage to 53 children.

Judged on the basis of cure-rate on 16 children, egressin® in relatively high dosage was of no value. It did, however, apparently decrease slightly the frequency of egg-deposition.

A standard seven day course of gentian violet produced cures in at least 80% of 33 heavily infested children.

The rate of spontaneous apparent cure was found to be related to the frequency of positive tests during the initial period of observation.

Investigations of remedies for pinworm infestation yield more conclusive results if conducted on selected patients whose rate of spontaneous apparent cure is more or less predictably low.

Acknowledgment

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SPANISH ABSTRACT

Tratamiento de la Infección por Oxiuros (Oxiuriasis) con Diphenan®, Egressin® y Violeta de Genciana

No hay en la actualidad un tratamiento satisfactorio conocido para la oxiuriasis pues aunque la cura el violeta de gencina, debido a la reinfección, los períodos en que el niño está libre de síntomas son cortos y los tratamientos repetidos con dicho medicamento son resistidos debido a los trastornos gástricos que produce y la necesidad de usar tabletas entéricas que deben ser tragadas enteras ya que generalmente el enfermo es un niño. Por otra parte las medidas higiénicas, aunque provechosas para prevenir la reinfección, son demasiado molestas para llevarse a cabo por largos periodos.

En vista de que el p-bencilfenil carbamato (Butolan, Diphenan) y el Egressin (3-metil-6-isopropilfenilester del ácido N-isoamilcarbámico) se han catalogado como medicamentos que no tienen las objeciones anteriores los autores decidieron probarlos conjuntamente con la violeta de genciana en un estudio comparativo de su eficacia habiendo llegado a las siguientes conclusiones:

1° Se diagnosticaron y vigilaron los enfermos por periodos variables por medio de la técnica de la tela adhesiva de celulosa, previamente al tratamiento con Diphenan, Egressin y violeta de genciana y después se siguieron vigilando por 6 ó mas días. Veinticuatro niños fueron estudiados en igual forma pero no se les dió tratamiento.

2° El Diphenan no demostró tener acción antihelmíntica alguna en 53 niños en quienes se usó a dosis altas.

3° Juzgando sobre la base del índice de curación en 16 niños, el Egressin en dosis relativamente altas no fué de valor, sin embargo, sí produjo, aparentemente, ligera disminución de la frecuencia de la puesta de los huevecillos.

4° Un tratamiento standard de 7 días con violeta de genciana produjo la curación cuando menos en el 80% de 33 niños infectados masivamente.

5° El índice de curaciones espontáneas aparentes estuvo en relación con la frecuencia de los exámenes positivos durante el período inicial de observación.

6° Las investigaciones a propósito de medicamentos para los oxiuros dan resultados mas concluyentes si se realizan en pacientes seleccionados cuyos índices de curaciones espontáneas aparentes pueda predecirse que sean más o menos bajos.

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CONGENITAL FIBROMYXOSARCOMA OF OS CALCIS

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SARCOMA of bone in the newborn infant occurs rarely enough to justify the report of a case. Arey,[1] in a recent review of malignant neoplasms in early life, stressed the high incidence of sarcoma in childhood, but statistical studies indicate that the prognosis of many malignant neoplasms of early life is encouraging. An early diagnosis of these neoplasms followed by prompt courageous action may alter an apparently unfavorable prognosis.

Malignant neoplasms of bone constitute an important cause of death in later childhood. They may be divided into osteogenic sarcoma and Ewing's tumour of bone. They are distinct pathologic entities, but their clinical and roentgenologic differentiation is not always possible. Osteogenic sarcoma refers to a bone-forming tumour but sarcoma is derived from ancestral osteoblasts. These cells may cease their differentiation at any point from primitive mesenchyme through the normal sequence of differentiation of bone to fibroblast, cartilage cell or osteoblast, with the resulting variations in the histologic pattern of the tumour. The intercellular matrix may vary from a myxomatous to collagenous, cartilagenous, osteoid or calcified osseous tissue. Attempts to separate the osteogenic sarcomas into different categories on the basis of their constituent types of cells or matrix, or on their gross anatomic location in the bone are of little, if any, clinical value.

The treatment of sarcoma of bone in the young patient consists of a course of radiation followed by amputation.

A survey of the literature revealed very few reports of congenital sarcoma in an extremity. Chamberlain and Lawrence[2] reported two cases, one a myxosarcoma of the foot and the second, a fibrosarcoma of the forearm. The extremities of these patients were amputated with good results, the first child being alive 2 years, 4 months after operation, the second, 1 year, 8 months after operation. In the first case, myxomatous tissue predominated in the tumour and anaplastic tissue was less evident, with minimal cellular activity. In the second, anaplastic tissue was prominent in the tumour. Numerous mitoses and areas of necrosis indicated rapid growth. Neither case showed metastatic spread.

REPORT OF CASE

M. B., male, was born by normal spontaneous delivery at full term. Family history is negative aside from occurrence of diabetes mellitus in maternal grandfather. Two siblings are alive and well. He was well nourished and developed (wt. 3.4 kg.) and aside from swelling of L heel, examination was entirely negative.

He was admitted to the Hospital for Sick Children 13 days later for investigation of lesion of foot. Physical examination revealed a healthy male infant. Lower borders of liver and spleen were barely palpable as firm smooth surfaces. There was no demonstrable adenopathy. A firm swelling, involving posterior ⅔ of L foot (Fig. 1) was noted. It was tender and showed a bluish red discoloration,

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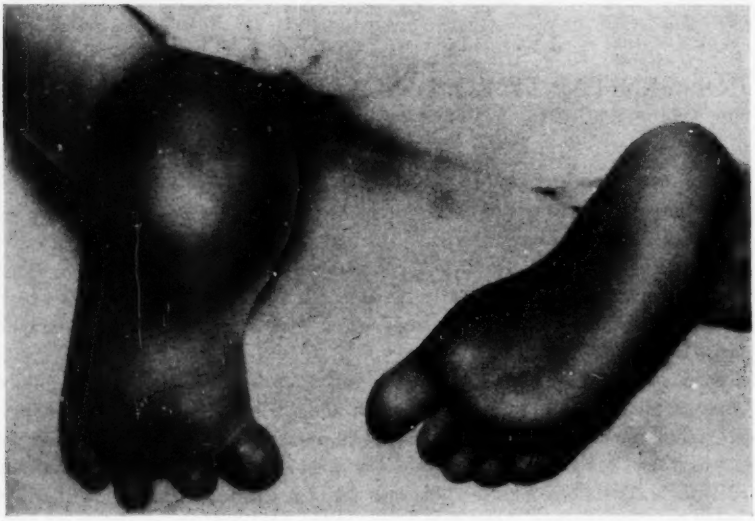

FIG. 1. Tumour of L foot.

resembling an hemangioma. Overlying skin was intact, tense and shiny. Neurologic examination was negative.

Roentgenologic examination by hospital radiologist, Dr. J. D. Munn, was as follows: "Chest and long bones, with the exception of the feet, reveal no unusual radiographic abnormalities. The bones of the left foot, particularly the astragalus, reveal marked destruction with some calcification of the soft tissues. The sunburst type of appearance and deposition of calcium with destruction of the os calcis suggest a vascular type of tumour." (Fig. 2.)

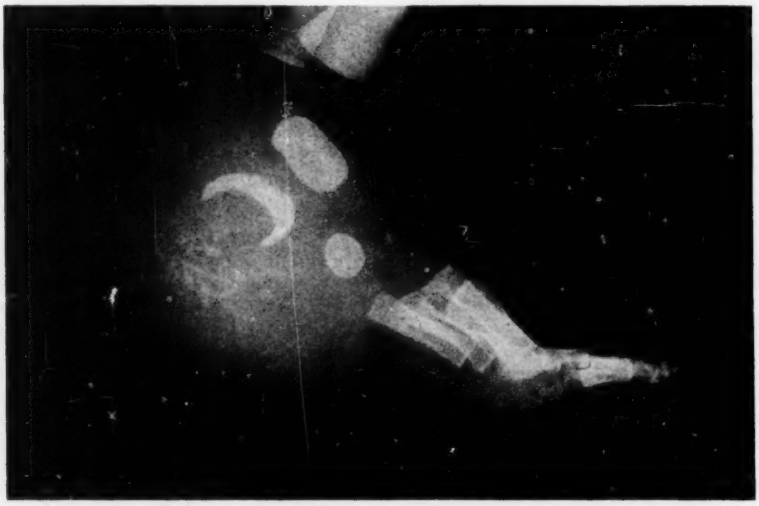

FIG. 2. RG of L foot showing marked destruction of bones, particularly astragalus, with some calcification of soft tissues.

A preoperative biopsy of the tumour was diagnosed by Dr. W. L. Donohue, hospital pathologist, as fibrochondro-osteosarcoma. In view of this report, Dr. A. W. Farmer, surgeon, performed an amputation of L leg below the knee 2 days after admission.

Pathologic report of gross specimen was as follows: "Specimen is a complete left foot and three inches of the lower tibia and fibula. The tumour is well circumscribed and limited to the ankle region. The cut surface is homogeneous and pale with a necrotic area measuring 1 cm. in diameter in the centre of the tumour."

Microscopic examination revealed a tumour composed of large fibroblasts arranged in wide bands and whorls. Cytoplasm is abundant in most places and is undergoing slight basophilic degeneration in some places. There are numerous foci of degeneration and calcification. Mitoses are few in number. (Figs. 3 and 4.) Diagnosis: fibrosarcoma (low grade).

Infant made an uneventful postoperative recovery in hospital. Healing of stump occurred by primary intention. Laboratory reports were normal. He has been examined at intervals of 3 mo.

FIG. 3. Photomicrograph of tumour which is invading cancellous bone. At top L corner is remnant of cortical bone. ×103.

without revealing any evidence of secondary metastases. Roentgen examinations of chest and long bones have been negative repeatedly. Repeated urine and blood analyses have been negative.

This patient, now 3 yr. of age, has developed normally in every respect, despite the handicap of an artificial limb. Psychologically, behaviour is average. Weight and growth curves have shown normal physiologic increases. His medical record subsequently has been uneventful.

DISCUSSION

The low malignancy of the tumour and the prompt, radical treatment may be credited for this apparently good result. There is no evidence of metastasis or recurrence after a three year period of observation.

Potter,[3] described a tumour in the forearm of a newborn infant, with immature fibroblasts, many of which showed mitosis, indicating malignancy, and diagnosed a spindle cell sarcoma. Disarticulation at the elbow resulted in a cure. This tumour, involving the radius and ulna, is probably of a type similar to that described in this report.

Lichtenstein[4] defines fibrosarcoma of bone as a primary malignant fibroblastic tumour which, upon thorough histologic sampling, fails to exhibit any tendency to form osteoid

and bone, either in its local growth or metastasis. It usually starts within the interior of the affected bone, most commonly involving the lower end of the femur. Eventually, the tumour tends to penetrate the overlying cortex, extending into contiguous periosteum and muscle. In dealing with the less serious central fibrosarcomas, any procedure short of amputation, especially in a child, is likely to prove unsuccessful. Eventual metastasis, particularly to the lungs, is inevitable, but much slower than in osteogenic sarcoma. The fibroblastic group of neoplasms require further study. The precise nature of the tumour, determined by biopsy, governs the therapy and prognosis, irrespective of the roentgenologic appearance of the lesion. Multicentric tumours of the nature of fibrosarcoma

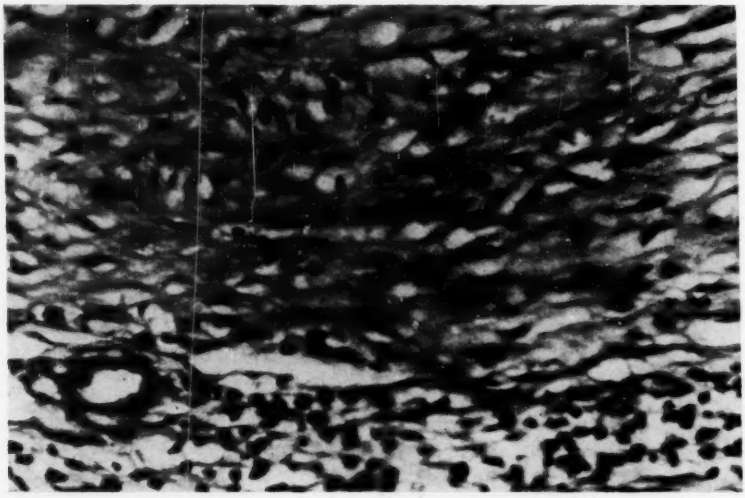

FIG. 4. Margin of tumour. In lower part of photomicrograph is normal marrow tissue. Neoplasm is obviously of low grade malignancy. ×311.

may develop within the visceral soft parts as well as the skeleton, as demonstrated by Steiner's[5] case in a 47 year old man with multiple diffuse fibrosarcoma with visceral metastases and a fatal termination after 10 months.

Central or medullary fibrosarcomas of bone present wide variation in growth potential and aggressiveness, behaving more like osteogenic sarcoma. Those arising from the periosteum are usually slow growing, show a lack of conspicuous pleomorphism of their connective tissue stroma and a disposition to local occurrence.

The classification of bone tumours by the American College of Surgeons in 1939 includes under the osteogenic series, fibrosarcoma, and under chondral series, both chondrosarcoma and myxosarcoma. Ewing[6] classifies fibrosarcoma, both medullary and periosteal, as a group of tumours that differs from the main varieties of osteogenic sarcomas. These tumours arise from within the marrow cavity or on the surface of the periosteum, grow slowly and are acellular and fibrous in structure. Recovery frequently follows local excision or amputation of the extremity. Their main features consist of the predominance of intercellular material over cells and low vascularity, with large spindle cells in bundles lying in an abundant fibrous matrix. The histologic picture of this group indicates low

vitality and very moderate malignancy, explaining the good prognosis following surgical intervention.

This case report emphasizes the fact that there are relatively benign osteogenic tumours, both medullary and periosteal, which offer an excellent opportunity for successful surgical treatment of a lesion, which is considered hopeless by many casual observers.

Summary

A case of congenital fibromyxosarcoma involving the os calcis, successfully treated by amputation, is reported. The rare occurrence of bone tumours in the newborn period is noted and a brief review of cases reported in the literature is given. The nature of these tumours, which are of relatively low malignancy, is discussed. Early diagnosis, by roentgen examination and biopsy study, followed by prompt, effective surgical treatment offer the best chance for a successful outcome.

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Spanish Abstract

Fibromixosarcoma Congénito del Astrágalo

En vista de su rareza se presenta un caso de sarcoma en un recién nacido, sano y bien conformado; con una tumoración firme en los dos tercios posteriores del pie izquierdo, que radiológicamente se interpretó como consecutiva a lesiones destructivas y de calcificación de los huesos del pie, particularmente del astrágalo. Aunque el patólogo catalogó el tumor como no maligno, se practicó amputación de la pierna izquierda, arriba de la rodilla. Hasta la edad de tres años el niño no ha mostrado metástasis secundarias. La poca malignidad del tumor y el tratamiento rápido y radical son los factores de este buen resultado.

El lado práctico de este informe está en no olvidar los tumores osteogénicos, tanto medulares como perióstico, relativamente benignos y curables con éxito por la cirugía. El diagnóstico se confirma tanto radiológicamente como por biopsia.

167 College Street

THALASSEMIA IN NEGROES

Report of a Case of Cooley's Anemia in a Negro Child

By L. Otto Banks, M.D., and Roland B. Scott, M.D.
Washington, D.C.

SINCE Mediterranean anemia was separated from the complex known as von Jaksch's anemia by Cooley and Lee[1] in 1925, the concept of the disease has undergone many changes. In the classic severe form, the disease is characterized by occurrence in peoples of Mediterranean origin, high familial incidence, mongoloid facies, splenomegaly, cardiac murmurs and icterus. Hematologically, these patients show low hemoglobin values, low color index, refractoriness to iron therapy, increased resistance of the erythrocytes to hypotonic solution of sodium chloride, presence of erythroblasts and target cells in the peripheral blood, and hyperplasia of the bone marrow.

At present the requirements for the diagnosis of this condition are less rigid than those described above. The most important diagnostic findings[2] are hypochromic anemia and decreased fragility of the red blood cells. Many mild cases which show typical and distinctive blood changes and absence of roentgenographic and clinical manifestations have been reported. The nonspecificity of target cells is well known.[3, 4] The absence of nucleated red cells in the syndrome has been reported.[5] A change in the Mediterranean racial concept is necessary due to the increasing number of cases being described in individuals of other ethnic groups.[6] It is difficult to definitely eliminate the possibility of remote admixture of other racial groups with those of Mediterranean stock.

The authors have found seven cases of Cooley's anemia in Negroes[4, 5, 7, 8] reported in the American literature. Three of these cases were in children.[5, 7, 8]

This report is a study of the disease in a two year old Negro male. He is the youngest case reported in this racial group. The patient's blood has been studied electrophoretically and the genetic ancestry of this child has been traced through four generations.

Case Report

S. S., a 2½ yr. old Negro male, was born in another hospital with a birth weight of 3.3 kg. The 25 yr. old Negro mother reported that labor, delivery and neonatal course of infant were uneventful. Developmental and feeding histories were normal and the only illness was rubeola at 10 mo. of age.

At time of admission to hospital history disclosed the following: Patient's eyes had been dark yellow for over a year; there were recent bouts of epistaxis and urine and stools had been dark brown for an indefinite period. Abdominal or joint pains, familial history of anemia or bleeding tendencies were denied. Physical examination revealed patient was well developed and well nourished. Sclerae were markedly jaundiced. Right posterior cervical glands were palpated. Heart was enlarged. A large spleen was present, extending down to level of umbilicus. Liver was not palpable. Clinical impression on entry was possible sickle cell anemia.

Hemogram revealed a moderate anemia and normal white blood cell count. Anisocytosis, poikilocytosis, numerous target cells and nucleated erythrocytes and hypochromia were observed in a smear of peripheral blood. A total of 60 slides utilizing various accepted methods[9–11] for sickling

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were all negative. These methods included the simple moist preparation, B. subtilis technic of Singer, exposure of carbon dioxide, sodium bisulfite and venous stasis technic of Waugh. Parameter test of Winsor and Burch[12, 13] was also negative.

Urine was dark brown, negative for blood and bile and strongly positive for urobilinogen. Stools were dark and were negative for blood, parasites and ova.

Average of 5 determinations of icterus index was 38 units. Fragility studies on 4 occasions showed increased resistance to hypotonic saline. Hemolysis began at 0.44% and ended at 0.20% (control 0.44 to 0.34) NaCl. Evidence of regeneration of blood was obtained from reticulocyte count which averaged 2.3%. On one occasion 42 nucleated red blood cells were counted/100 white blood cells. Bone marrow examination revealed a pronounced normoblastic response.

Patient received a therapeutic trial of ferrous sulphate for 2 wk. No change in RBC count, hemoglobin, nucleated red cells, reticulocytes or bone marrow picture was noted during or in 4 wk. after this therapy.

Diagnosis

Patient had a hemolytic anemia and the long history of jaundice and presence of enlarged hard spleen indicated that it was a chronic hemolytic anemia. Sickle cell anemia can be ruled out by absence of sickling using methods previously mentioned. Blood of the parents and other relatives also did not sickle. Absence of spherocytes and decreased fragility of erythrocytes to hypotonic saline solution did not point to congenital hemolytic anemia. Thin and thick blood smears made on 4 consecutive days were negative for malarial parasites. Heterophile antibody test and febrile agglutina-

Fig. 1. A. Lateral view of skull RG showing hazy appearance of maxillae.
B. Chest RG shows cardiac enlargement.

tion series on 2 occasions were negative. There was no history of ingestion of paint, chemical agents or allergy. Coomb's test for indirect antibodies, cold hemaglutinins and the Donath-Landsteiner tests were negative. Two Eagle tests and 2 Kahn tests on patient's serum were also negative.

This Negro child represents a true case of Cooley's anemia. Peripheral smears of blood showed numerous target cells, occasional oval cells in conjunction with anisocytosis, poikilocytosis and anisochromia. Basophilic stippling was not demonstrated. Abnormal fragility test showing an increased resistance to hypotonic saline is strongly in favor of diagnosis of Cooley's anemia. High incidence of cellular abnormalities found in this family also favors this diagnosis. Roentgenograms of skull (Fig. 1) revealed clouding of maxillae and early thickening of diploe in frontal bone. Heart was enlarged (Fig. 1). Films of long bones showed some demineralization and coarsening of trabeculae (Fig. 2). Bones of hands exhibited swollen melted appearance described by Caffey[14] who reviewed the roentgenograms and agreed with the diagnosis (Fig. 2).

Presence of target cells in patients with liver disease has been reported.[2] Because of long-standing jaundice in this case, liver function studies were done. Cephalin-flocculation tests performed on 2 occasions were 3 + in 24 hr. and 4 + in 48 hr. Thymol turbidity was 10 units and a 4 + flocculation

in 18 hr. Both of these tests point to liver damage. However, serum proteins, cholesterol, alkaline phosphatase and prothrombin time determinations were normal. The authors believe that the liver damage present was secondary to long-standing hyperbilirubinemia due to the hemolytic disease. Abnormal fragility tests and high incidence of hematologic abnormalities in family of this patient are strongly in favor of the anemia as being the primary factor in causing liver damage.

Genetics

The parents presented typically Negroid features and no history of Caucasian admixture could be obtained. Abnormalities in blood of patient, his mother, father, maternal grandmother, maternal great-grandfather, maternal aunt, uncle and paternal grandmother are delineated in chart 1. On all members of this family tested, 4 moist slide preparations were made using the methods of Singer and Robin and Dagland and Castle. Sickling could not be elicited in any relative of the patient.

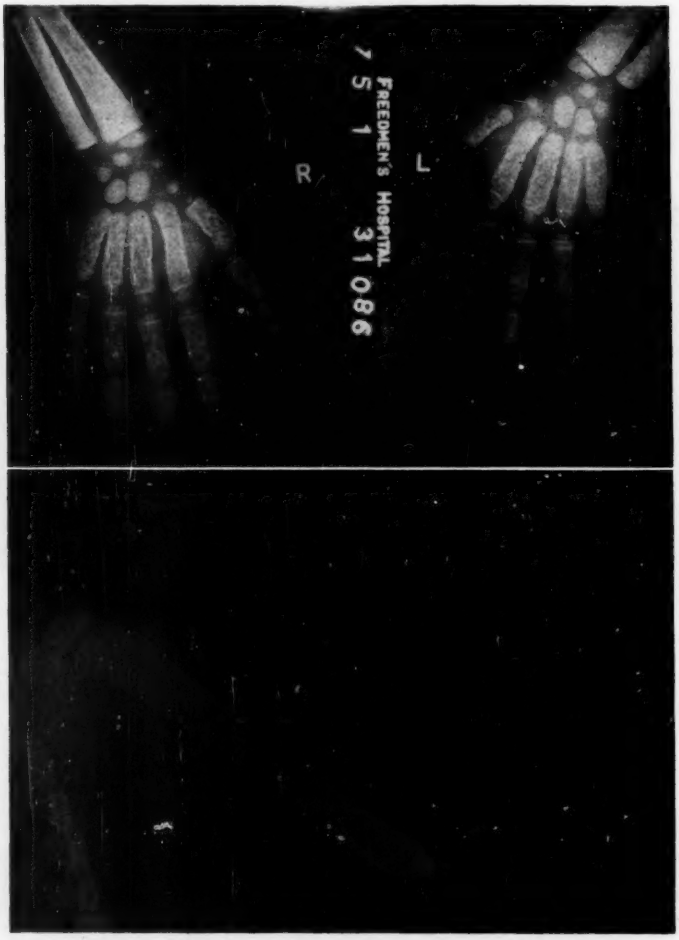

Fig. 2. Marked coarsening of trabeculae and demineralization is noted in RGs of upper extremities with spectacular findings in bone of hands.

Blood of the 27 yr. old mother, an American Negro, showed numerous target cells, hypochromia and abnormal fragility. She exhibited no hematologic response to a 2 wk. trial on iron therapy. Numerous attempts to demonstrate sickling were all negative. She represented a case of thalassemia minor (trait).

The 36 yr. old father is a native of the British West Indies. Presence of target cells, anisocytosis, poikilocytosis and abnormal fragility test represents also the trait or thalassemia minor state. His first marriage with a spouse whose blood showed no abnormalities produced 2 sons whose bloods were normal on basis of studies performed.

Maternal grandmother, great grandfather and aunt and uncle have hematologic and fragility findings which are suggestive of the thalassemia minor state. Paternal grandmother, although not anemic, showed numerous target cells, microcytosis, anisocytosis, poikilocytosis, abnormal fragility test and a high reticulocyte count.

On the mother's side the great-grandfather who has the trait married a normal female and it was he (great-grandfather) who passed the trait down to the grandmother. She in turn passed it on to several other children, including mother of the present patient. Studies were not done on the grandfather who died in an automobile accident. On father's side although only one person could be tested; his mother possesses the Cooley's trait.

Electrophoretic Analysis: Electrophoretic determinations were performed by Itano[35] on the hemoglobins of parents and patient. Each lacked any sickle cell hemoglobin and showed a pattern compatible with those found in Cooley's trait, Cooley's anemia and in normal individuals. Under the conditions of the study (Ph 6.5 in cacodylate buffer of ionic strength 0.1 employing carbonmonoxyhemoglobin) it was not possible to differentiate Cooley's hemoglobin from normal hemoglobin.

The information from this study did not rule against a diagnosis of Cooley's anemia and Cooley's trait in the child and his parents, respectively. On the positive side, it produced further evidence against the presence of sickle cell anemia.

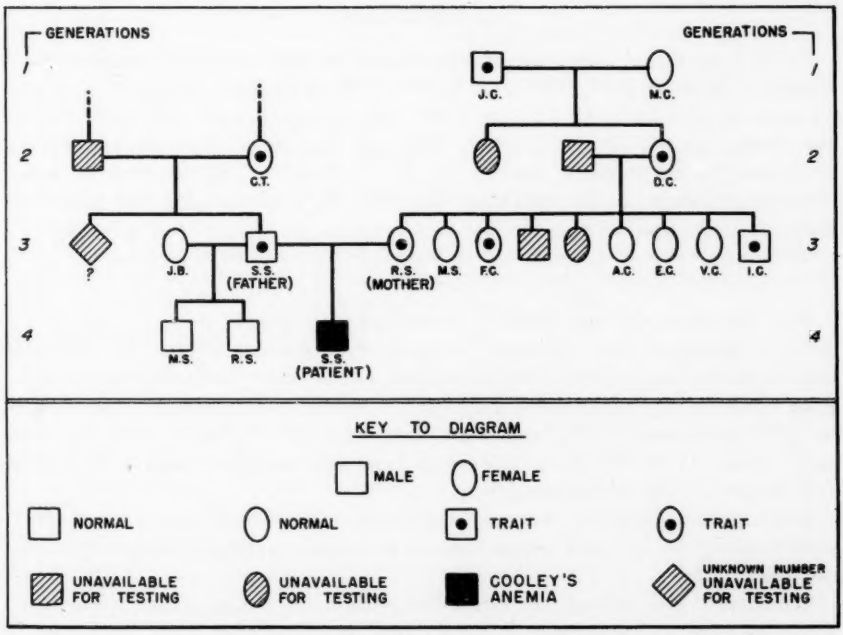

CHART 1. Family tree of patient with Cooley's anemia. It is noted that 7 of his antecedents bore Cooley's trait.

Discussion

The fact that each generation tested in this family showed thalassemia minor and that both parents possess the trait is in keeping with the homozygous-heterozygous theory of Neel.[16-18] This theory has been postulated to explain the genetic pattern in Cooley's anemia and in sickle cell anemia. According to Neel the asymptomatic trait is due to a gene which is represented but once in the individual's genetic system (heterozygous state) whereas the active disease appears when the gene occurs twice (homozygous).

The parents are Negroes of different nationalities. The mother is American and the father is British West Indian. No evidence of Caucasian blood admixture can be obtained in either parent, although unknown and remote admixture cannot be absolutely eliminated. The concept of Cooley's disease as occurring only in Mediterranean peoples must be revised. In cases reported in other racial groups, the possibilities of admixture of Mediterranean stock cannot be completely eliminated. However, the finding of the trait in the Negro population indicates Cooley's anemia may be much more common in this group than is realized.

Summary

A case with typical features of Cooley's anemia is reported in a two year old Negro male. Thalassemia minor was found in each generation of this family and could be traced down to the patient. The fact that both mother and father have the trait is compatible with the homozygous-heterozygous theory of Neel.

Acknowledgments

Dr. Jack Rheingold, consultant in hematology, Freedmen's Hospital, examined blood smears on the entire family. Dr. James A. Wolff, Babies Hospital, New York City, gave valuable advice in this study. Dr. John Caffey, Babies Hospital, New York City, reviewed the roentgenograms. Dr. H. A. Itano, California Institute of Technology, Pasadena, performed the electrophoretic studies. Dr. Althea Kessler of this department assisted with the preparation of the manuscript. Dr. Hilda M. Bolden referred the patient for study.

Addendum

Since the manuscript was submitted, patient has had additional study. On January 15, 1953, a splenectomy was performed because of the following reasons: (1) persistent anemia necessitating frequent blood transfusions, two of which were followed by troublesome reactions; (2) progressive enlargement of spleen which eventually extended into the pelvis and caused marked abdominal protuberance and lumbar lordosis; (3) slow weight gain; (4) fear that this grossly enlarged and abnormal organ would be traumatized and ruptured by the child's play activity.

Recovery from splenectomy was prompt and without complication. There was an anticipated transient rise in certain formed elements of the blood (platelets, nucleated red cells and leukocytes).

Condition of child during past 4 months (postoperative) fully justifies splenectomy. There has been an improvement in weight gain, general comfort, body posture and a decreased need for blood transfusions.

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SPANISH ABSTRACT

Thalasemia en los Negros

Se presenta el caso de un niño de dos años de edad de la raza negra con manifestaciones típicas de anemia de Cooley. Se encuentra sintomatología de la misma en todas y cada una de las generaciones de la familia hasta el paciente y en vista de que tanto el padre como la madre la padecen, los autores aceptan su compatibilidad con la teoria homozigo-heterozigótica de Neel.

Sixth and Bryant Streets, N.W.

INCIDENCE OF HYPERTENSION IN POLIOMYELITIS

By MEYER A. PERLSTEIN, M.D., MORTON B. ANDELMAN, M.D., DAVID C. ROSNER, M.D., AND PAUL WEHRLE, M.D.
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THE concept that acute anterior poliomyelitis is a disease involving only the spinal cord, and occasionally the brain, and whose sequelae are limited to lower motor paralysis of isolated muscle groups, is no longer tenable. To the contrary, it has been shown that poliomyelitis may affect not only all levels of the central nervous system, but also non-nervous tissues; e.g., heart, kidneys, liver.[1]

The recent work by Baker[2] and others[3] has demonstrated that all levels of the brain and spinal cord as well as the autonomic nervous system may be involved. When the brain stem and midbrain are involved, symptoms referable to these areas may become manifest.

This preliminary report deals with the incidence of hypertension in the acute and convalescent stages of poliomyelitis. Interest in the subject stems from an experience with a case in which hypertension was a prominent and permanent finding.[4] Involvement of the reticular substance of the bulb was found at autopsy. In reviewing the literature on the occurrence of hypertension in poliomyelitis, one is impressed with the apparent infrequency of this association.

Grulee and Panos,[5] in an epidemic of poliomyelitis in Minneapolis in 1948, observed transient hypertension in the first week of the disease which persisted for an average of 3.4 days in 51 of 70 cases of bulbar poliomyelitis (72%). In 41 cases of the spinal paralytic form of the disease, they found the blood pressure elevated in 18 (44%). In 36 cases of nonparalytic poliomyelitis hypertension was noted in 14 (39%). It was their impression that damage to the vasomotor control centers in the brain was the primary factor in its causation. Unfortunately, in the 70 cases of bulbar poliomyelitis in which the incidence of hypertension was highest (72%), information is not available on the division of their case material according to severity or type of bulbar involvement. In addition, no mention was made of the urinary findings in their cases. Baker, Matke and Brown[2] studied in detail the brains of 80 cases of bulbar poliomyelitis from the Minneapolis epidemic of 1948. They found damage to the large reticular cells located in the ventromedial area in those cases with clinical symptoms of vasomotor disturbances including blood pressure changes.

Sennett, Perlstein, Andelman, Barnett and Josephy[4] reported on a case of poliomyelitis with protracted hypertension in whom recent changes in the region of the reticular substance were found at autopsy. They inferred that involvement of the vasomotor centers and lateral horns was responsible for the hypertension. Although pyelonephritis developed as a complication, they believed that this alone was not sufficient to account for the hypertension in their case. Hypoxia, likewise, was ruled out as the prime factor in pro-

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ducing the hypertension. Salus[6] reporting on three cases of hypertension associated with poliomyelitis, considered the inflammatory changes in the brain stem, especially in the region of formatio reticularis, to be an important factor in producing hypertension.

McDowell and Plum[7, 8] published their observations on 95 patients with poliomyelitis of whom 45 developed hypertension (47%). Of the total group reported, only nine were nonparalytic, and of these only one had hypertension. However, their cases may be a selected group, as indicated by the high incidence of paralysis and the preponderance of adults (youngest case 10 years). Devic[9] has also reported two siblings with fatal poliomyelitis in whom hypertension occurred. Both of these cases had involvement of the brain stem.

Present Study

Present report covers an observation of 195 cases of poliomyelitis at the Municipal Contagious Disease Hospital of Chicago and the Michael Reese Hospital of Chicago from July 1950 through December 1950. In addition to usual history, physical examination and spinal fluid studies, repeated muscle evaluations and repeated blood pressure readings were made during the acute as well as convalescent stages of the disease. Patients were observed in the hospital for periods ranging from 10 days to 4

TABLE 1

Normal Blood Pressure in Children*

(From Mitchell and Nelson[10])

Age (yr.)	Systolic mm.Hg	Diastolic mm.Hg
4	85	60
5	87	60
6	90	60
7	92	62
8	95	62
9	98	64
10	100	65
11	105	65
12	108	67
13	110	67
14	112	70
15	115	72
16	118	75

* Standard deviation ±5 to 8 mm.Hg.

mo. Since fluctuations in blood pressure incident to fright or anxiety are greater in the systolic phase, the diastolic blood pressure was utilized as the more constant and thus more reliable reading. Diastolic blood pressure as listed in Mitchell-Nelson[10] (table 1) was used as the norm. An increase in diastolic pressure of 15 mm.Hg or more above the average was considered indicative of hypertension. This is more than 2 times greater than standard deviation for these norms (5 to 8 mm.Hg) (table 1).

Repeated urinalyses were done on all patients, and urea clearance and blood-urea nitrogen and creatinine determinations were made on most of those having hypertension. Abnormal urea-clearance tests or elevated blood-urea nitrogen levels were not obtained in any case.

Results

Two-thirds of the 195 patients were paralytic (133) and one-third (62) nonparalytic; two-thirds (130) had no elevation and one-third (65) had definite evidence of elevated

TABLE 2

DISTRIBUTION OF CASES BY INCIDENCE OF HYPERTENSION AND PRESENCE OF PARALYSIS

Clinical Diagnosis	No. Cases	No. with Hypertension	%
Nonparalytic	62	8	13
Paralytic	133	57	43
Nonrespirator cases	114	48	42
Respirator cases	19	9	47
Total cases	195	65	33

blood pressure at some time during the course of the illness (table 2). It can be seen that the incidence of hypertension was over three times as great in the presence of paralysis (43% of 133 cases) than in its absence (13% of 62 cases). It was noted that the incidence of hypertension was not related to the presence of respiratory difficulties, since in both the group with and without respiratory difficulties the incidence of hypertension was close to 45%. This would indicate that anoxia or respiratory embarrassment *per se* probably is not a primary factor in the causation of hypertension.

On the assumption that neurologic involvement in areas controlling vasomotor functions might be responsible for the hypertension, one might expect to find a greater incidence of hypertension in patients with high cervical involvement than in those with low cervical involvement. This is not borne out by the findings. From table 3 it is noted that the incidence of hypertension in patients with upper-extremity involvement differs little from that with lower-extremity involvement. Although the highest incidence of hypertension occurred in the 22 patients with intercostal involvement (55%), the number of cases is not large enough from which to draw definite conclusions. It will also be noted that the incidence of hypertension was not significantly different in cases with bulbar or encephalitic involvement than in those from the general group with paralysis.

The authors were unable to find any consistent findings which would indicate kidney

TABLE 3

HYPERTENSION AND LOCALIZATION OF PARALYSIS

Site	No. Cases	No. with Hypertension	%
Extremities	55	22	40
Upper extremities alone	11	4	36
Lower extremities alone	28	12	43
Upper and lower combined	16	6	40
Intercostal	22	12	55
Bulbar	43	19	44
Encephalitic	7	3	43
Total	133	57	43

damage. Their experience in general corroborated that of Grulee and Panos[5] that the hypertension was of a transient type, lasting 2 to 4 days. McDowell and Plum[7] reported that blood pressure elevation in their series lasted an average of 5½ days in those patients not requiring artificial respiration, and an average of 98 days in those who were respirator cases. In two patients in the series reported here the blood pressure remained elevated for prolonged periods. One was a 21 year old boy with congenital syphilis and a familial history of hypertension. His blood pressure was normal before his illness, and the elevation at this date has persisted for over one year, varying from 150/100 to 200/120 mm.Hg. He has a residual palsy of the right arm. The other patient was an 8½ year old girl who had all four extremities and the intercostal muscles involved. It was necessary to place her in a respirator for one week. On admission on the third day of illness her blood pressure was normal, but became elevated by the sixth day, when it was 156/120 mm.Hg. It persisted in an elevated stage for over two months. At the end of this time she was discharged and no follow-up report has been available.

Although the minimal rise in diastolic pressure in this series was 15 mm.Hg (empirically), the average diastolic rise was 29 mm.Hg and the highest 63 mm.Hg.

Comment

As to the possible factors which might predispose to a transient hypertension in acute poliomyelitis, the following must be considered: (1) disturbed renal function; (2) anoxemia; (3) psychogenic factors; (4). involvement of the vasopressor center in the brain stem. We can be fairly certain that the kidney does not play any measurable part in the hypertension, for repeated urinalyses and blood chemistry determinations of blood, such as blood urea-nitrogen and urea-clearance tests, were normal.

Anoxemia, although possibly playing a secondary role, particularly in respirator patients, was not considered as a primary agent in the production of hypertension in these cases, as it occurred in patients without respiratory involvement. The authors did not determine the oxygen-saturation of arterial blood, but clinically no evidence was found to suspect anoxemia in either nonparalytic or paralytic patients with hypertension. Moreover, in the case reported by Sennett et al.,[4] where blood-oxygen and carbon-dioxide studies were done, no evidence of anoxia was found.

One might suspect that in older children psychogenic factors incident to their illness might cause sufficient tension to cause hypertension. However, hypertension in this series was found with equal frequency in infants and young children as in older children and adults. To exclude further the possibility that emotional factors incident to hospitalization or to the presence of an acute infectious disease might have a nonspecific effect in causing hypertension,[11] blood pressure readings were taken on infants and children who were hospitalized for other acute diseases. Of 67 such patients, no blood pressure readings approached the authors' arbitrary figure of diastolic abnormality (15 mm.Hg above the average), indicating that diastolic pressure is much less labile than systolic as a result of emotional factors.

Baker, Matke and Brown,[2] in a detailed histologic study of the brain stem in 80 cases of bulbar poliomyelitis, found that pathologic changes could be correlated with clinical findings. They found that damage to the large reticular cells located in the ventromedial reticular area was invariably associated with clinical symptoms of vasomotor disturbances. Bodian[3] has repeatedly emphasized that generalized involvement of the central nervous

TABLE 4

ANNUAL INCIDENCE OF HYPERTENSION IN POLIOMYELITIS

	No. Cases		% Hypertension	
	1950–1951		1950–1951	
Total	195	247	33	21
Paralytic	133	161	43	29
Nonparalytic	62	86	13	6

system exists in poliomyelitis even when little is to be found clinically. This might explain the transient hypertension encountered occasionally in a case of nonparalytic poliomyelitis. In an attempt to determine whether lability of the sympathetic system might be implicated, the authors performed cold-pressor tests on these patients. In no instance was an abnormal rise in blood pressure observed in either the patients with or without hypertension.

In the follow-up study now being completed for the year 1951,* it is apparent that the incidence of hypertension in poliomyelitis will be much less than found in 1950 (table 4). McDowell and Plum[7] reported on the poliomyelitis patients admitted during the years 1949 and 1950, in whom 47% had hypertension. However, since they grouped their cases for 1949 and 1950 together, the present investigators are unable to compare the 1950 findings with their results. In the second year (1951) of this observation, hypertension was observed in 52 (21%) of 247 cases. Of 161 with paralysis, 47 (29%) had hypertension. Of 86 (35%) nonparalytic, 5 (6%) had hypertension. Thus it would appear that the occurrence of hypertension in poliomyelitis may vary in its incidence from year to year. This may explain why the observation that hypertension may occur in poliomyelitis has not been previously emphasized.

SUMMARY

Hypertension is a frequent occurrence in poliomyelitis. In a 1950 epidemic in Chicago it occurred in about one-third of all cases.

Hypertension was generally of transitory nature, although in two instances it was prolonged.

Hypertension was three times more frequent in patients with paralysis than in nonparalytic patients. It was most common in respirator cases.

The incidence of hypertension was not related to the localization of paralysis, emotional factors, anoxia, sympathetic system involvement or kidney involvement. Therefore, it is inferred that it is probably of central origin.

ACKNOWLEDGMENT*

The authors are indebted to the members of the pediatric staff of the Sarah Morris Hospital for the privilege of including their private cases in this study.

* The material for the 1951 polio season is now being analyzed and will be presented in detail in a subsequent report.

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SPANISH ABSTRACT

Incidencia de Hipertensión en Poliomielitis

Ya no es posible sostener el concepto de que la poliomielitis anterior aguda sea una enfermedad que afecte exclusivamente la médula espinal y ocasionalmente el cerebro, y cuyas secuelas se limitan a la parálisis motora periférica de un grupo aislado de músculos. Por el contrario, se ha demostrado concluyentemente que tanto cerebro como médula pueden ser afectados en distintos niveles e igualmente el sistema nervioso autónomo.

Este informe de los autores trata acerca de la incidencia de la hipertensión arterial en el período agudo y de convalescencia de 195 casos de poliomielitis observados durante la epidemia de 1950 en la ciudad de Chicago.

Las observaciones realizadas pueden resumirse en la siguiente forma: 1° La hipertensión arterial es frecuente en la poliomielitis y se presentó casi en una tercera parte de los casos. 2° Generalmente fué de carácter transitorio aunque hubo dos casos en que fué prolongada. 3° Fué tres veces más frecuente en los enfermos con parálisis que en los casos no paralíticos y común en los pacientes que requirieron respirador. 4° La incidencia de la hipertensión no tuvo relación con la localización de la parálisis, factores emocionales, anoxia, lesión del sistema simpático o del riñón, por lo que se infiere que sea probablemente de origen central.

4743 North Drake Avenue

A HEARING TEST FOR NEWBORN INFANTS

By JULIUS B. RICHMOND, M.D., HERBERT J. GROSSMAN, M.D., AND SEYMOUR L. LUSTMAN, PH.D.
Chicago

INCREASING interest in the earlier placement of infants for adoption has made accurate evaluation of the physical and sensory status of the newborn infant a primary responsibility of the physician. It was the present authors' objective, therefore, to develop a practical, readily reproducible test for neonatal hearing which may be employed routinely by the clinician.

HISTORICAL REVIEW

The original concept that the newborn infant was insensitive to auditory stimulation as held by Kussmaul[1] was disproved by Genzmer[2] in 1873 and by Liebmann[3] in 1900. Since that period, the auditory sensitivity of the neonate has been well substantiated by numerous investigators.[4–14]

It is now quite apparent that even *in utero,* the fetus will react with demonstrable movements to sound stimulation. This was first reported by Forbes and Forbes,[15] and later was more carefully studied by Ray[16] who attempted to condition a fetus to sound and vibration applied to the maternal abdomen. Performing 214 experiments on seven women, Sontag and Wallace[17] demonstrated that fetal response to sound was detectable about the thirty-first week of intrauterine life and was increased in magnitude of response as term approached.

In 1928, faced with an adoption problem, Aldrich[18] conditioned pain in the form of a pin-scratch on the sole of the foot to the sound of a dinner bell in order to demonstrate hearing in a three month old infant. In the study of conditioned responses, a number of psychologists have used auditory stimulation. Thus hearing was incidentally demonstrated in the first 10 days of life by Marquis,[19] who successfully conditioned sucking and quietening to the sound of a buzzer. Conditioning to sound was also demonstrated by Razran,[20] Wenger[21] and Kantrow.[22] It must be pointed out that performing such conditioning experiments poses an intricate problem. From 1 to 5 days is required to produce the desired response, thus rendering the procedure too complex and time-consuming to be used as a screening test with the newborn infant. The electroencephalogram also represents a valuable but complex method for testing.[23]

Bryan,[24] in 1930, using a hand-bell and a series of Galton whistles, studied 75 infants in their first 10 days of life. He found that the reactions of blinking, startling, stirring, crying and opening of eyes was erratic, but he concluded that many newborn infants give evidence of hearing from the third to the seventh day on. Froeschels and Beebe[14] obtained no reaction to tuning forks, but found that whistles produced the most frequently observed palpebral reflex. It must be emphasized that these studies for the most part are aimed at exploring infant-response patterns, and not at the development of testing procedures.

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Experimental Procedure

Forty-six infants from the University of Illinois Research and Educational Hospital nursery were used in this study. Of these 39 were full-term infants ranging from ½ hr. to 8 days of age. Seven were premature infants ranging from 1 to 15 days of age. Each infant was classified into the following testing conditions: (1) light sleep, (2) deep sleep, (3) awake, (4) active nursing and (5) post-stimulation comprising those infants from other groups who did not respond to the first auditory stimulation. Infants in Groups 4 and 5 were tested under 2 of the above conditions.

An auditory stimulus was accomplished by striking a bell held about 33 cm. from infant's head. Bell was of the standard percussion "cowbell" variety, having an intensity of 113 decibels at a distance of 33 cm. with 2 dominant overtones 2,650 and 8,000 cycles/sec., respectively. Such bells are available from most musical supply shops. Each infant was stimulated an average of 3 times and observed by 2 observers for reaction to sound. Palpebral and/or startle reflex was taken as evidence of hearing in the infant. Palpebral response was interpreted as a cochlear-palpebral reflex in which blinking of open eyes or a further tightening of lids if the eyes are closed occurred in response to sound stimulus. Some workers consider the startle response as a variant of the Moro; however, Hunt[25] stresses extensor characteristics of the Moro as contrasted with flexor characteristics of the startle. For the authors' purposes, any sudden movements of the trunk or extremities were considered a startle response.

It must be noted that results are in terms of gross hearing and do not take into account the possibility of varying degrees of hearing defect which may be discovered at subsequent examinations of the older child.

All infants who did not respond to the above procedure were stimulated to the point of arousal by gentle skin massage over the back or the abdomen and immediately retested.

It soon became apparent that the infant who was actively crying did not respond to any stimulation. The procedure was therefore modified to testing infants only while they were relatively quiet.

Results

The results, which are summarized in table 1, are as follows:

1. All 46 infants in this series gave evidence of hearing in the form of a positive palpebral and/or startle response when tested under the conditions of light sleep, awake, and post stimulation. Although the infants ranged from ½ hour to 8 days of age when tested, this series reveals no significant differences in terms of gross hearing which were referable to variations in age within this group.

2. The palpebral response seemed to be the most significant response, since it was positive in 70% of the observations, whereas the startle response was positive in only 47% of the observations. However, the use of both is very effective since the presence of one and/or the other was observed in all cases.

3. The best condition under which to test neonatal hearing is light sleep, since the highest percentage of positive responses is observed under this circumstance.

4. The poorest conditions under which to test for neonatal hearing are active crying, deep sleep, and active nursing. Six of the 24 infants tested in deep sleep and 3 of the 6 infants tested while actively nursing gave no evidence of response to the sound stimulus. Under other conditions, all nine of these infants responded to sound.

5. Of the six infants in deep sleep who gave no evidence of hearing, all responded to sound when immediately retested after having been stimulated to the point of light sleep or arousal by gentle massage over the back or abdomen.

6. It is interesting to note that the only circumstances in which no startle responses were elicited was during active nursing by the infant. Four of these 6 infants manifested startle responses under other circumstances. Further investigation is under way to determine how nursing has the effect of raising the threshold to sound to some extent. The fact

TABLE 1

NEONATAL REACTION TO AUDITORY STIMULATION

Condition	No. of Infants	No. of Infants Responding with Palpebral and/or Startle	Response	Observations % Positive
Light sleep	13	13	Palpebral	94%
			Startle	88
			Total	91%
Deep sleep	24	18	Palpebral	56%
			Startle	33
			Total	45%
Awake	9	9	Palpebral	83%
			Startle	52
			Total	67%
Active nursing	6	3	Palpebral	33%
			Startle	0
			Total	17%
Poststimulation	6	6	Palpebral	85%
			Startle	46
			Total	65%
			Total Palpebral	70%
			Total Startle	47%

that palpebral responses were obtained suggests that other factors besides threshold to sound may be involved.

DISCUSSION

Because of the relative inconsistencies of results of earlier investigations, it was the object of the authors to determine whether a consistent, valid test for hearing in the newborn could be developed. This report presents the results of 292 observations on 46 newborn infants which, it is believed, offers a reliable yet simple test of hearing in the neonate.

The authors believe that the use of the palpebral and startle responses is an effective combination as criteria for neonatal hearing, and that the key to testing hearing in the newborn infant lies in the state of arousal and awareness of the infants when tested. This would seem to suggest that the newborn is only capable of responding consistently to auditory stimuli when his maximal energies are not diverted to such consuming activities as eating, deep sleep or crying.

The authors recommend that the following procedure be followed as a screening test for sensitivity to sound in the physical examination of every newborn infant:

1. The neonate should be tested for hearing only when reasonably quiet, and never while in a deep sleep, actively nursing or crying. Light sleep seems to be the optimal condition under which to test for hearing.

2. The use of a percussion "cowbell" as described is suggested as a readily available and consistent sound stimulus; the palpebral and startle responses are simple observations which may be used in combination for evidence of hearing.

3. Infants manifesting no response should be retested after stimulation at the point of light sleep or arousal by light massage on the skin of the back or abdomen.

4. If the neonate does not respond to this screening procedure, more elaborate conditioning experiments or electroencephalographic examinations are indicated. In the authors' experience with 46 newborn infants, none required this additional examination.

Since surveys of hearing in children indicate that the incidence of congenital deafness is of the order of 65 to 70/1,000,000 population,[26] it was not statistically probable that a congenitally deaf child would be discovered in this study. It would seem likely, however, that this test procedure would identify such infants in the newborn period. Inasmuch as complete deafness is usually not detected until the latter part of the first, and sometimes not until the second year of life, it seems reasonable to suggest that this test for hearing be made a part of the physical examination in the newborn nursery. It is probable that such routine testing in the nursery would give accurate statistical data concerning the incidence of true congenital deafness at an early age.

Summary

A simple, readily reproducible test of gross hearing in the newborn infant is presented. Although the test is particularly applicable to adoption problems, it is suggested that this examination be adopted as standard procedure in all nurseries as a part of the routine evaluation of the neonate.

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SPANISH ABSTRACT

Un Prueba de Percepción Auditiva en los Recién Nacidos

Los autores presentan una prueba práctica y fácil para probar el sentido del oído que ayude al clínico en su responsabilidad para recomendar la adopción de recién nacidos y como rutina en su examen general.

Hicieron la prueba en 46 niños, 39 nacidos a término y con una edad de media hora a ocho días y los otros 7, prematuros de uno a quince días de edad. La prueba se realizó en las siguientes condiciones: (1) Sueño ligero, (2) Sueño profundo, (3) Despiertos, (4) Durante su alimentación, y (5) Repitiéndola en aquellos niños que no respondieron a la primera excitación auditiva.

La excitación auditiva se realizó a 25 centímetros de distancia con una campana que presentaba una intensidad de 113 descibeles y dos tonos dominantes de 2650 a 8000 ciclos por segundo respectivamente. Se excitaba al niño en tres ocasiones observándolo dos médicos simultáneamente; se tomó como prueba de percepción auditiva el reflejo palpebral y/o el reflejo de estremecimiento. Con esta observación se investiga una percepción auditiva gruesa, y no la fina que puede descubrirse en exámenes subsecuentes de los niños mayores.

Todos los niños dieron señales de oir cuando se les examinó en el sueño ligero, en la vigilia y con una segunda excitación, sin diferencias significativas para la edad. En el 70% fue positiva la respuesta palpebral mientras que la del estremecimiento en el 47%. La mejor respuesta se tuvo en el sueño ligero y las peores cuando los niños lloraban, comían ó dormían perfectamente; en casos negativos todos respondieron inmediatamente a la segunda excitación, cuando se les repitió en sueño ligero así como cuando dejaban de llorar o comer.

Los autores consideran que las respuestas palpebrales y de estremecimiento son útiles como criterio para determinar la percepción auditiva de los recién nacidos si la prueba se realiza en los niños despiertos o en sueño ligero, y la recomiendan como de utilidad en la valoración general del recién nacido.

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AMERICAN ACADEMY OF PEDIATRICS, INC. PROCEEDINGS AND REPORTS

Round Table Discussion

PEDIATRIC X-RAY DIAGNOSIS

EDWARD B. D. NEUHAUSER, M.D., Boston, *Chairman*

PIERCE D. KNOTT, M.D., Sioux City, Iowa, and BRICK P. STORTS, M.D., JR., Tucson, Iowa, *Secretaries*

Chairman Neuhauser: I have been very much impressed with the pediatricians who know much more about diseases and abnormalities of the heart and lungs than they give themselves credit for, but the roentgen manifestations of abnormalities of the gastrointestinal tract do not appear to be as well understood. Many of the lesions that occur in the gastrointestinal tract, even the common ones, are overlooked. An understanding of the simple lesions and many of the more complicated ones is essential if the proper roentgen examination is to be carried out.

Most of the congenital malformations that occur have a rather simple embryologic explanation. There is defective recanalization of the fetal gut. When the fetal gut is first formed it is an open tube, but during the first few weeks of fetal life there is proliferation of the epithelial lining cells with obliteration of the lumen. Recanalization promptly ensues.

Many of the abnormalities occur during this process of recanalization. Stenosis, atresia, diverticular, duplication and many of the fistulas have their origin during this period of recanalization. The very simple lesions of stenosis and atresia are best demonstrated by lantern slides.

Tracheo-esophageal fistula without atresia or stenosis of the esophagus is not at all uncommon. Many are overlooked because the condition is not suspected; others may be overlooked because the roentgen examination is not properly carried out. Certainly a fistula between the esophagus and trachea running obliquely upward from the anterior aspect of the upper third of the esophagus to the trachea cannot be visualized if the patient is examined only in the supine or prone position. The patient must be examined in the lateral projection so that the trachea and esophagus are seen without superimposition and so that the opaque medium has an opportunity of passing through the fistula into the trachea. Occasionally the fistula itself cannot be identified, but flooding of the trachea by the opaque medium may be seen.

Dr. Maxwell P. Borovsky, Chicago: We had an experience here at Cook County Hospital with a baby about 2 months of age. It had episodes of apnea and dysphagia on feeding, but only when

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it was being fed did it have this difficulty. We tried some ordinary physiologic studies and got nowhere. We very fortunately have a good congenital cardiac set up with Dr. Gasul. We suspected that there might be a congenital malformation of the heart. We took a number of spot films and there was one film that showed a communication between the trachea and esophagus. The interesting thing about this was that the fistula was against gravity, running upward from the esophagus to the trachea with the consequence that there wasn't much of an aspiration because of the upward route of the food. That baby was operated on very successfully.

Chairman Neuhauser: It is of the utmost importance for the pediatrician to have the courage of his convictions if a fistula is suspected. A single negative examination cannot be relied upon to exclude this abnormality. I well recall one patient where the fistula was not demonstrated until the third examination.

When examining the esophagus radiographically the correct choice of opaque medium is important. For the ordinary routine examination of the esophagus where no particular lesion is suspected, we ordinarily use a thin barium sulphate paste flavored with chocolate and sweetened with sugar. However, in small infants this cannot be satisfactorily used and a thin barium fed by spoon or through the feeding bottle is more satisfactory. We now only employ iodized oil in the presence of a known or suspected atresia of the esophagus and we no longer use it in a search for an isolated tracheo-esophageal fistula as the difficulty of the examination is increased when iodized oil is used as most infants are unable to properly swallow the oil and a considerable amount passes through the larynx into the trachea.

I feel that no examination of the esophagus in an infant or small child should be carried out unless a suction machine is at hand in the fluoroscopic room. We have had to use the suction machine on many occasions and I am convinced that we would have lost several if the suction machine had not been immediately available.

Congenital stenosis of the esophagus occurs primarily in the upper third. Only rarely is a stenosis of the lower third congenital in origin. It is more apt to be acquired from esophagitis. Stenosis of the upper esophagus may produce in addition to dysphagia respiratory signs and symptoms as the dilated upper esophageal segment may produce considerable encroachment upon the lumen and displacement of the trachea.

Atresia of the esophagus is certainly well known to you. The results of surgical treatment are getting better all the time and I think that we can look forward to a survival rate of at least 75%. The rather typical signs and symptoms suggest the diagnosis. Constant drooling of saliva and immediate regurgitation of feeding should suggest the diagnosis and the proper roentgen examination should be carried out. This examination is not only important in establishing the diagnosis, but it is also of an aid in determining the length of the atretic segment, the exact site of the atresia and the presence or absence of a fistula. Under fluoroscopic guidance a catheter should be passed into the upper esophagus and a few cc. of warm iodized oil instilled. The patient should be turned into the lateral decubitus in an attempt to visualize a fistulous communication between the upper esophagus and the trachea. A fistulous communication between the trachea and lower esophagus can naturally be diagnosed by the presence of gas in the gastrointestinal tract. If there is no lower fistula the atretic segment is apt to be unduly long and surgical correction very much more difficult.

Duplications of the esophagus are not uncommon. The signs and symptoms produced may be variable or signs may be absent unless there is pressure or encroachment upon adjacent structures. They usually appear as small or large cystic masses which will vary somewhat in shape during change in position and are found in close juxtaposition to the esophagus, but may not deform or displace the esophagus very much. I personally have not as yet seen one where there was a communication between the esophagus and the duplication.

Question: When you see a case like this how do you make the diagnosis?

Chairman Neuhauser: The diagnosis cannot be made with certainty as the appearance can be simulated by other lesions, particularly a cystic hygroma of the mediastinum.

It is possible to have combinations of duplication, stenosis or atresia and fistula and one must be prepared for bizarre abnormalities and combinations.

All the lesions that we have discussed so far can also occur in the intestinal tract. The use of an opaque medium is rarely necessary in most patients with severe stenosis or atresia of the bowel. Although it is not always possible to make an exact diagnosis as to the type of atresia, it is usually

possible to estimate the degree of obstruction and to localize the obstruction within reasonable limits, so that definitive surgical treatment can promptly be carried out.

Duplications associated with the small bowel are very difficult to recognize as they may produce no or only minimal displacement of the adjacent bowel. However, those in association with the distal ileum may produce intussusception with its typical clinical and roentgen findings. Occasionally a duplication may calcify. Duplications and even triplications of the colon have been reported.

During the past few years it has become evident that lesions of the esophagus in young infants are common and important. However, it is equally clear that at the moment the nature and origin of all these lesions is not well understood. There is a group of abnormalities that have as a common denominator relaxation of the lower esophagus with free regurgitation of gastric content into the esophagus. One may find simple relaxation of the hiatus portion of the esophagus, gastric hiatus hernia, para-esophageal hiatus hernia and apparent extension of gastric mucosa into the lower esophagus. Although on occasion the exact nature of the primary abnormality cannot be determined with certainty, the regurgitation and relaxation of the hiatus can be identified. Because of this resultant esophagitis and peptic ulceration of the lower esophagus leading to spasm, shortening and stenosis may occur. In our hospital, ulceration of the lower esophagus is very much more frequent than ulceration anywhere else in the intestinal tract.

The roentgen signs of hypertrophic pyloric stenosis are too well known to require much elaboration here, but unfortunately during the past few years there has been an unfortunate tendency to attempt shortcuts to avoid the necessarily rather laborious procedure which must be carried out to establish an exact diagnosis. One cannot rely on film examination alone and we believe that dependence on opening time of the pylorus or emptying time of the stomach is likewise unreliable. The diagnosis can be made with certainty only by demonstration of the narrow elongated pyloric canal on spot films. The examination should be carried out in a normal physiologic manner with barium mixture administered by mouth as if the stomach is filled by catheter many of the important lesions of the esophagus will be overlooked.

The roentgen diagnosis of meconium ileus is frequently difficult and occasionally impossible. However, approximately three-quarters of the patients with this abnormality present a rather characteristic roentgen picture. There are multiple dilated loops of small bowel and in the distal loops of ileum the meconium may be outlined by numerous bubbles of gas that have been forced into this tenacious mucilaginous material that blocks the bowel proximal to the ileo-cecal valve. The colon is usually free of gas and fecal matter. The appearance may be mimicked by fecal impaction in the proximal colon or by inspissated meconium in the distal ileum, and if the abnormal meconium cannot be identified on the film the picture may be similar to or identical with that produced by an atresia or severe stenosis of the distal ileum. It may be necessary to carry out a barium enema to localize the obstruction. By this means an infantile Hirschsprung's disease can be clearly differentiated as in the presence of meconium ileus a micro-colon will be present. A micro-colon is naturally a colon that has not as yet functioned. It appears short and extraordinarily narrow as to lumen. However, unless the colon is aganglionic normal function will properly ensue after the obstruction has been corrected.

In association with obstruction of the bowel one may find intrauterine perforation with extrusion of epithelial cells and calcific deposit about these epithelial cells outlining a portion of the peritoneal cavity. This must be distinguished from the calcific deposit that may occur in meconium or in the wall of an atretic bowel segment.

Question: What is this calcification due to?

Chairman Neuhauser: I don't know what it is due to, but we do know where it is. It is calcific deposit about the extruded epithelial cells. It can occur very promptly and according to reports within 24 to 48 hours. If the patient survives the calcific deposit tends to disappear, although in one instance I know that a portion has still been present at the end of 4 years. In addition to the calcific deposit, numerous adhesions are present.

Question: What do you do for meconium ileus patients after you have made the diagnosis?

Chairman Neuhauser: There are many things that can be done, but survival is still unusual. It is usually necessary to do an ileostomy, milk out as much of the abnormal meconium as is possible and to lavage the bowel with pancreatic solution or saline.

New Speaker: When our patient was operated on, the surgeon used saline in and around the meconium and he was able to free the bowel. The child has advanced pancreatic fibrosis and we

come back to the question of whether we should do anything for the patient with meconium ileus. As far as I know they go on and develop the full blown disease and only live 2, 4 or 6 years.

Chairman Neuhauser: That is, of course, true. I think that even with our present knowledge we should make every effort to pull these patients through their initial obstruction as our knowledge of this disease is increasing and the results of more modern treatment of the pulmonary changes has led to considerable success.

First Speaker: It is difficult whatever you do and the prognosis is not good.

Question: I frequently have parents call me on the phone and say that their child has swallowed a foreign body of some sort. Shall I rush him right over to the hospital for x-ray film? Do you feel that these foreign bodies should be x-rayed to discover just where the object is, or are we justified in waiting 48 hours to see if the child passes the object?

Chairman Neuhauser: I personally feel that you had better get a film. Certainly a foreign body should not be allowed to remain in the esophagus and it is wise to identify the location and the type of foreign body swallowed. Many are quite innocuous, but others, such as open safety pins or bobby pins, are likely to produce trouble. I would hazard a statement that more of our patients are operated upon for removal of a bobby pin than any other foreign body as these pass the duodenojejunal junction only with difficulty.

Question: What about the plastic toys the children play with and sometimes swallow—are they opaque?

Chairman Neuhauser: Nearly all of them are nonopaque.

Question: One of the problems that we encounter in children from 4 to 8 years, and we see a few every day, is pain in the abdomen. On examination it appears to us that it is associated with anxiety, but we invariably get a report back from the radiologist that it is a pyloric spasm. Have you seen the same thing and is there a definite picture of it?

Chairman Neuhauser: I doubt very much if there is such a thing as pyloric spasm as an isolated lesion. However, I am sure that you can get pyloric spasm with gastric ulceration or with ulceration of the duodenum and true hypertrophic pyloric stenosis may occur in association with ulcers close or near to the pyloric canal. Certainly the child with abdominal pain is a difficult problem and in many instances we are never successful in elucidating the nature of the complaint. In addition to lesions of the gastrointestinal tract which should be excluded, it is truly important to exclude a hidden lesion of kidney, and I believe it wise to carry out an intravenous urogram if all other studies have not been helpful.

Symposium

BASIC MECHANISMS IN ALLERGIC DISEASES

BRET RATNER, M.D., New York City, *Chairman;* T. N. HARRIS, M.D., Philadelphia; MILTON G. BOHROD, M.D., Rochester, N.Y.; ADOLPH ROSTENBERG, JR., M.D., Chicago

RECENT DEVELOPMENTS IN THE CELLULAR TRANSFER OF HYPERSENSITIVITY AND ANTIBODY FORMATION

T. N. HARRIS, M.D.

This review will describe certain developments which have appeared recently in the immunologic literature involving the transfer of viable cells from one animal to another. In 1940 Landsteiner and Chase showed that it was possible to remove cellular exudates from guinea pigs sensitized with simple chemical compounds, wash these cells and transfer them to fresh guinea pigs and then to demonstrate in the recipient guinea pigs dermal sensitivity to the original compound. More recently, Dr. Merrill Chase sensitized guinea pigs with o-chlorobenzoyl chloride: paraffin oil had been injected intraperitoneally into these animals 48 hours before, in order to induce the necessary cellular accumulation. These cells were collected, washed and injected into a recipient guinea pig, which thereupon developed a positive reaction to the allergen.

Similar experiments were done with cells secured from lymph nodes of sensitized guinea pigs and in the case of heat-killed tubercle bacilli suspended in hydrocarbon as antigen.

The same phenomenon has been demonstrated by Metaxas with intradermally injected cells, and by Lawrence in the human species with leucocytes collected from blood and injected intradermally.

Tissue reactions of the immediate type of hypersensitivity have also been demonstrated by Chase as a function of transferred cells by the use of the Schultz-Dale technic, as well as by an adaptation of the PK type of reaction to the measurement of classical antibodies.

It was felt in our laboratory that this type of approach might provide more direct information on the mechanism of antibody formation in the cells involved. Accordingly, a study of such cells was undertaken, using largely bacterial cells as antigens and measuring the agglutinins produced thereto. The hind foot pads of rabbits were injected with 0.2 cc. of a 0.5% suspension of Shigella paradysenteriae, previously killed by exposure to alcohol, and 4 days later—at a time when the popliteal lymph node is known to contain antibody—the animals were killed and the lymph nodes excised. The cells of the nodes were gently teased into salt solution with fine dissecting needles. The lymph nodes were generally large and swollen and as the teasing was begun streams of whitish material would pour out into the surrounding fluid. The cells were collected, washed and injected into recipient rabbits. The sera of the recipient animals showed some agglutinins on the first day after transfer, and an increase in titer on the 2nd day. The peak titer usually occurred on the 3rd or 4th day, after which there was a plateau for a few days, with a decline in titer beginning at about the 7th day. The serum titer had usually returned to its pre-injection level between the 28th to 40th day after transfer.

The effectiveness of such transferred cells in causing the appearance of antibody in the recipient animal could be prevented by any of the following treatments of the cells: freezing and thawing in a dry-ice-alcohol bath, incubation overnight at 37°C., ultraviolet irradiation, injection into species other than the rabbit (guinea pig, embryonated hen's egg), and exposure to alcohol. It was felt that the appearance of antibody in the serum of the recipient rabbits was not due to active immunization or to passive immunization, but probably to some function of the transferred cells.

PATHOLOGY OF THE ALLERGIC AND COLLAGEN DISEASES

MILTON G. BOHROD, M.D.

The pathologic changes found in allergic disease are probably never pathognomonic. There are, however, characteristic findings which show varying degrees of necrosis, exudation with edema,

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granuloma formation, or homogenizing change in collagen. If each of these changes is selected for classificatory purposes and the allergic and related diseases be assigned in the classification according to the predominant change, a classification such as that in table 1 may be constructed. This table shows also the experimentally produced states and the (probably) nonallergic conditions which show similar histologic findings. Table 2 indicates that each of these groups has important clinical and immunologic correlations.

TABLE 1

	Examples in Human Pathology	Examples in Experimental Pathology	Nonallergic Mechanisms Which May Produce Changes
Necrotizing			
Tissue selective	Cortical necrosis of kidney; acute pancreatic necrosis	Arthus and Schwartzman phenomenon	Primary drug injuries
Cell selective	Thrombocytopenic purpura; granulocytopenia	Antiplatelet serum	Primary drug injuries; overwhelming infection
Anaphylactoid	Serum sickness; asthma and hay fever; atopic dermatitis; glomerulonephritis; periarteritis nodosa	Experimental anaphylaxis; experimental nephritis, etc.	All mechanisms producing *stress* (Selye)
Granulomatous			
Tuberculoid	Tuberculosis; brucellosis; tularemia, etc.; beryllium granulomas	Experimental infections with same organisms	Probably *none*
Rheumatoid	Rheumatic fever; rheumatoid arthritis; "giant-cell" rheumatoid granulomas	?	Mechanisms of stress and diseases of adaptation (Selye)
Hyalinoid			
Collagen diseases	Disseminated lupus erythematosus; dermatomyositis; scleroderma	None known	Mechanisms of stress and diseases of adaptation (Selye)
Amyloidosis	Amyloidosis	Parenteral injection proteins or nucleic acids	Neoplasms (multiple myeloma). Others?

Necrotizing lesions resemble the Arthus and Schwartzmann reactions. They may select specific tissues or pick out single specific cells in a tissue, as for instance in the bone marrow. One source of sensitizing substances responsible in the induction of this group of lesions is probably auto-antigens, which lead to auto-immunization.

Anaphylactoid lesions are predominantly exudative, sometimes almost exclusively edematous. They make up the bulk of the lesions which are treated by the practicing allergist. Eosinophilia is a common finding in the peripheral blood, in exudates and in the tissue lesions.

Granulomatous lesions may resemble those of tuberculosis (tuberculoid granulomas) or of the rheumatoid diseases (rheumatoid lesions). The similar histologic picture of tuberculoid lesions is the result of the similar allergic state which exists in all of them; a similar skin test for all of them, when appropriate antigen is used, is a clinical correlate of this fact. The purely histologic diagnosis of tuberculosis is no longer justified and the etiologic agent of tuberculoid granulomas must be sought by bacteriologic methods. Rheumatoid granulomas occur around joints, in skin, and in eyes and viscera. The lesions in the lining of joints is often nonspecific.

The collagen diseases are probably only in a minority of cases allergic, unless auto-antigens will be found to be responsible in this group. Periarteritis nodosa represents a disease which shows characteristics about equally divided between the collagen diseases and the anaphylactoid states. The lupus erythematosus cell is a distinct advance in the diagnosis of one of this group: lupus erythematosus. Plasmacytosis and hyperglobulinemia are frequent findings. When they reach their most marked degrees, amyloidosis is a possible end-result.

One of the characteristic features of all the foregoing groups is their tendency to be associated together. Typical periarteritis nodosa occurs with asthma and with rheumatoid arthritis; granulomas with periarteritis nodosa (Wegener's granuloma); all of these with amyloidosis; and innumerable other combinations. Similarly, histologic lesions of one group may be found to some degree in any of the other groups. This frequent co-existence is evidence that they share mechanisms in common and that, in some fashion, they belong together in one classification.

TABLE 2

CORRELATION BETWEEN HISTOLOGIC CLASSES AND CLINICAL AND IMMUNOLOGIC PHENOMENA IN ALLERGIC DISEASES

	Type of Clinical Reaction	Clinical Course (Velocity)	Duration	Skin Reaction	Antibody in Serum	Increased Serum Globulin	Specific Infection	Eosinophilia	Necrosis
Necrotizing	Immediate	Rapid	Short	0 or + Necrosis	0 or +	0	0 or +	0 or +	++++ (Diffuse)
Anaphylactoid	Immediate	Rapid	Short to moderate	Wheal type	Frequently +	Usually 0		+ to ++++	+ (Fibrinoid)
Granulomatous									
Tuberculoid	Delayed	Variable	Short to long	Tuberculin type	0	0 to +++	+	0	++ (Caseous)
Rheumatoid	Delayed	Slow	Long	0	0	0 to ++	0	0 or +	++ (Fibrinoid)
Hyalinoid									
Collagen disease	Delayed	Variable	Short to long	0	0	++	0	0 or +	++ (Fibrinoid)
Amyloidosis	Delayed	Slow	Long	0	0	+ to ++++	0	0	0

PHYSIOLOGIC MECHANISMS OF ANAPHYLAXIS AND ALLERGY

BRET RATNER, M.D.

Allergy is a battle against the invasion into the body of foreign substances that are inhaled, ingested or injected. The body is so constructed that it continually impedes the invasion into the circulation of materials that cannot be utilized. When the organism fails to prevent the entrance of inimical agents, allergy may ensue.

The major role in allergy is played by the antigen-antibody tissue reaction. The union between antigen and fixed cellular antibody (sessile antibody) produces cellular irritation which results in physiologic disturbances of the affected tissues.

For example, in serum sickness the antigen must be present either in the circulation or within the cells in order to bring about the reactions with early formed antibodies.

We believe that histamine does not play a major role in the resultant physiologic pathology of the phenomenon under discussion but, if anything, a very minor one.

It might be stated that the wheal is the ultimate unit of the allergic reaction. The basic mechanism and genesis of wheal formation, however, is not fully understood.

We postulated that wheal formation would be a sudden constriction of the arteriole resulting in a fall in arteriolar pressure—the stoppage of blood to the venules with its sudden back flow—increased pressure on the endothelial lining of the venules and lymph structures with a transudate into the surrounding tissue and wheal formation.

When unstriated muscle is stimulated or irritated by any means, whether it be chemical, hormonal, neural, physical or by the union of antigen and specific antibody, the only response that such smooth muscle can have is to contract.

The type of syndrome that is evoked depends upon the characteristics of the tissue affected. Thus, if the involuntary muscle of the arteriole contracts, if bronchioles become spastic, if the hepatic venules become stenosed, if perineural vessels are affected, if the unstriated muscle of the gastrointestinal tract is involved, one can readily see how different must be the resultant physiologic and pathologic disturbances. It enables us to conceive how the varied gamut of syndromes such as serum sickness, eczema, urticaria, hay fever, asthma, disturbances of the gastrointestinal tract, central nervous system involvement and the profound liver changes and changes in other organs may transpire. All these apparently diversified manifestations therefore come about from a single basic phenomenon, namely, a spasm of one or another of the many involuntary muscle structures in the various tissues. All this bears witness to the widespread distribution of sensitized tissue cells.

Although many tissues are affected, the major reaction dominates and overshadows all others, for it is the vital organ that contains the most strategically located smooth muscles that produces the major reaction in a given allergic episode.

With our present knowledge, were we to accept the histamine concept of the allergic phenomena, or the newer endocrine concept inherent in the use of ACTH and cortisone, or the dominant role of the psyche as the primary modus operandi of the allergic reaction and put aside the antigen-antibody mechanism, I believe there would be little hope for more than symptomatic relief of the allergies.

It is the study of the many ways and means that antigens have of invading the body and producing interactions with tissue-fixed antibodies which offers the greatest hope for a thorough understanding of the basic mechanism of the allergic phenomena. The contributions based solely on the antigen-antibody concept have given us a profound insight into the fundamental nature of allergy.

SOME OF THE MECHANISMS BY WHICH DRUGS AND ANTIBIOTICS PRODUCE REACTIONS

ADOLPH ROSTENBERG, JR., M.D.

Too often when a patient takes a drug and some reaction develops, it is alleged that the patient is allergic to the drug in question without any evidence being offered to support that designation. Actually, there are many mechanisms by which drugs can produce reactions other than via an allergic sensitization. The accompanying table lists some of the known mechanisms.

Mechanism	Example
I. Pharmacologic	
a. acute	Ergot gangrene
b. chronic and cumulative	Argyria
II. Enzymic Interference	
a. vitamin deficiency-like states	Pellagra
	Acrodynia
b. photosensitization	Sulfa light eruptions
	Pellagra
III. Idiosyncratic	Arsenical keratoses
	Iododermas
	Bromodermas
IV. Allergic	Penicillin "serum sickness"
V. Shwartzman	
VI. Herxheimer-like effect	"Penicillids"
VII. Ecologic	Monilial eruptions
VIII. Biotropic	Erythema nodosum

By pharmacologic is meant an effect that is known to be a property of the drug in question and would develop in anyone who took the drug in adequate dosage and for an adequate length of time.

By enzymic interference is meant that a drug either "poisons" a given enzyme system or that the drug competes with the system for a necessary component so that its proper functioning is impaired. Probably the pharmacologic effect of a drug is often arrived at by this means, but, in the present case, the enzymic interference is one that is neither anticipated nor desired.

By idiosyncrasy is meant an inborn deviation in the way that the individual will respond to a given stimulus. Both qualitative and quantitative aberrations are included, although these are sometimes separated.

By allergy is meant a specifically acquired alteration in the capacity to react brought about by means of an antibody mechanism.

By the Shwartzman phenomenon in this connection is meant the production of cutaneous lesions where the skin has been prepared by either the lodgement of bacterial toxins or the organisms themselves; subsequently the intravenous circulation of the same or other bacterial toxins or the occurrence of an antigen-antibody union causes the development of a hemorrhagic necrotic reaction in the prepared skin site.

A Herxheimer effect is defined as an accentuation of pre-existing lesions or the development of new ones, based on a too vigorous destruction of organisms so that either allergens to which the individual is sensitive or toxic materials are released.

By ecologic interference is meant that the drug, by virtue of destroying competitors of a given micro-organism, renders conditions more favorable for the propagation of the organism in question.

By biotropism is meant that the drug has a stimulating effect on certain micro-organisms latent within the individual.

It should, of course, be realized that there are probably other mechanisms by which drugs produce reactions and also that many of the mechanisms discussed are not mutually exclusive. Consequently, the same clinical manifestation might be brought about by more than one of the processes considered. Many of the definitions given require further amplification for the sake of clarity and precision, but in the space of this abstract this was not possible.

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Died Oct. 29, 1952—EMERITUS

Bernard S. Denzer
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Shelton, Conn.
Died Nov. 15, 1951—EMERITUS

Gerti Dooneief
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William W. Falkener
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Arthur E. Karlstrom
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Died Oct. 4, 1951

Alfred L. Kastner
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Died April 5, 1953

Earl W. May
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East Grand Lake
Alpena, Mich.
Died Dec. 16, 1952—EMERITUS

Guy S. Millberry
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Died Sept. 30, 1952—ASSOCIATE MEMBER

L. J. Osborne
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Owego, N.Y.
Died July 14, 1952—EMERITUS

Paul L. Parrish
52 S. Portland Ave.
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Died Jan. 29, 1953—EMERITUS

Louis S. Robins
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Died Jan. 8, 1953—EMERITUS

Richard Scammon
Fewacres
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Died Sept. 12, 1952—ASSOCIATE MEMBER

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Southold, L.I., N.Y.
Died Oct. 1952

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Died March 30, 1953—EMERITUS

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SPECIAL SECTIONS

PUBLIC HEALTH, NURSING AND MEDICAL SOCIAL WORK

MYRON E. WEGMAN, M.D., *Contributing Editor*

PREVIOUS discussions in this column have dealt with the problems surrounding adoption and the precautions and safeguards which should be used by all practicing physicians. The strong desirability of agency placement, to assure the kind of skilled social service necessary in adoptions, was emphasized. On the other hand, many physicians have not become reconciled to the long waiting periods and some of the other difficulties involved in working through agencies even though they are considered essential for full protection of the child, the natural parents, and the adoptive parents.

The Children's Bureau has recently released data indicating the extent to which, in 1951, the various methods were used in carrying out adoptions. Nearly half of the children adopted by persons not related to them were placed in adoptive homes independently of a social agency. Many of the children were very young and many of them born out of wedlock. This is the group particularly vulnerable to black or gray market practices. Even though there is no doubt but that some of these adoptions were successful, others were accompanied by difficulties and unhappiness for all concerned, difficulties which could easily have been avoided with proper planning.

The Children's Bureau report was prepared from data furnished by State Public Welfare Agencies, 25 of which furnished substantially complete information for 1951. On the basis of these reports the Bureau estimates that probably 80,000 adoption petitions were filed in the United States during the year. This is a 60% increase over adoption petitions filed in 1944. Large increases occurred both in the number of children adopted by persons not related to them and in the number of children adopted by step-parents or other relatives. It should be noted that in 1951 more than half the adoption petitions were filed by relatives of the child.

The report attributes the increase of adoptions to the large numbers of homes broken by death, divorce or desertion during and following World War II and to increase in the number of children born out of wedlock, a major source of adoptable children.

The average age of the children for whom adoption petitions were filed was 3.3 years.

TABLE 1

ADOPTIONS BY RELATION OF PETITIONERS

State	Total	Relation of petitioners to children				Relation not reported
		Own parent	Step-parent	Other relative	Not related	
Total.....						
Number.....	25,294	220	8,563	2,683	10,353	3,475
Per cent.....	100	1	39	12	48	—
Arkansas.....	499	6	150	71	271	1
Connecticut.....	982	15	369	74	504	20
Delaware.....	141	1	50	17	46	27
Florida.....	1,690	11	494	206	699	280
Georgia.....	996	6	242	160	556	32
Hawaii.....	627	18	277	104	212	16
Indiana.....	2,810	41	970	332	1,212	255
Iowa.....	1,645	2	635	155	828	25
Kansas	1,200	10	487	119	583	1
Kentucky.....	665	1	119	140	394	11
Louisiana.....	683	—	188	73	420	2
Maine.....	823	19	375	94	334	1
Minnesota.....	1,743	—	590	122	919	112
New Hampshire...	257	5	56	42	140	14
New Mexico.....	486	—	150	89	242	5
North Dakota....	255	—	111	20	121	3
Oregon.....	1,434	20	608	137	666	3
Puerto Rico.....	103	5	9	17	72	—
Rhode Island.....	392	16	228	42	105	1
South Dakota.....	286	2	90	23	170	1
Texas.....	4,432	20	1,352	343	106	2,611
Vermont.....	240	3	70	35	131	1
Virgin Islands.....	5	—	3	1	1	—
Virginia.....	1,429	18	387	165	808	51
Wisconsin.....	1,471	1	553	102	813	2

Two-fifths of the children were under 2 years of age at the time the adoption petition was filed.

In independent placements, more than 50% of the children were under one month of age at the time of placement, which means that in many instances these children were placed either directly from the hospital or shortly thereafter. Only 11% of the children placed by agencies were under one month of age. Agencies make studies of the background of adoptive parents, the natural parents, and the child, and also insure that legal requirements regarding the surrender of the child are met prior to placing the child. Such procedures are not usually followed in independent placements.

In the 25 states reporting complete information on adoption petitions, the number of adoptive children was almost equally divided between those born out of wedlock and those born in wedlock. Nonrelated persons filed adoption petitions for 69% of the adoptive children born out of wedlock but only 25% of those born in wedlock.

TABLE 2

ADOPTIONS BY TYPE OF PLACEMENT

State	Total	Type of placement				No placement made	Type of placement not reported
		Agency		Independent			
		Public	Private	By parents or other relatives	By others		
Total							
Number	25,294	2,349	3,827	4,071	2,870	9,380	2,797
Per cent	100	10	17	18	13	42	—
Arkansas	499	131	—	89	58	221	—
Connecticut	982	116	237	99	113	396	21
Delaware	141	2	—	36	23	53	27
Florida	1,690	—	280	241	458	711	—
Georgia	996	125	73	396	121	249	32
Hawaii	627	74	16	180	43	305	9
Indiana	2,810	553	177	485	136	1,221	238
Iowa	1,645	77	361	—	490	717	—
Kansas	1,200	25	111	245	250	567	2
Kentucky	665	80	111	154	52	254	14
Louisiana	683	38	157	—	225	261	2
Maine	823	57	59	—	—	—	707
Minnesota	1,743	167	706	132	80	581	77
New Hampshire	257	52	43	95	13	11	43
New Mexico	486	43	20	177	84	154	8
North Dakota	255	—	99	33	6	111	6
Oregon	1,434	—	217	69	379	765	4
Puerto Rico	103	10	1	71	5	16	—
Rhode Island	392	33	54	51	11	242	1
South Dakota	286	61	22	59	49	94	1
Texas	4,432	245	533	842	45	1,426	1,341
Vermont	240	31	66	54	12	67	10
Virgin Islands	5	5	—	—	—	—	—
Virginia	1,429	229	161	369	206	401	63
Wisconsin	1,471	195	323	194	11	557	191

Data not available for the states not listed.

Table 1 shows the number of adoption petitions filed in the 25 states reporting, and the relation of the adoption petitioners to the children. Table 2 shows the type of placement by which the adoption was made.

It is to be hoped that the Children's Bureau will continue and amplify reports of this type. The problems surrounding adoption procedures affect the happiness of children and parents and have become an increasing concern of pediatricians. Through continued careful evaluation of the factors involved in current practice it may be possible to find ways to simplify procedures without sacrificing essential safeguards.

NEWS AND ANNOUNCEMENTS

ANNOUNCEMENT OF AMERICAN ACADEMY OF PEDIATRICS' PEDIATRIC RESIDENCY FELLOWSHIPS

The American Academy of Pediatrics will grant 12 or more fellowships for pediatric residents for a period of 6 months to one year. These fellowships have been created to enable young physicians in financial need to complete their pediatric training. The fellowships carry a stipend of $500 to $1000 depending on the length of time needed to complete training and the need. The fellowships have been made possible by a grant to the Academy from Mead Johnson & Company and will be granted as of Jan. 1 each year. The deadline for receipt of applications will be Sept. 1, 1953.

Criteria for the awards will consist of the following: (1) a letter from the Chief of Service indicating that the proposed individual has completed, or will have completed by Jan. 1, 1954, one year of pediatric training credited by the American Board of Pediatrics; that the resident has performed his work ably; and that there is real need for financial assistance; (2) a letter from the resident requesting the fellowship stating that he intends to enter pediatric private practice at the conclusion of his second year of training. Consideration will be given to geographic spread of appointments, so that all sections of the country will be represented, and preference will be exhibited for well-qualified but smaller training centers which perhaps have fewer resources for assisting residents in training than do some of the larger centers. Note that research interests and accomplishments and desire to enter academic pediatrics are not criteria for the awards.

Members of the Committee on Residency Fellowships of the American Academy of Pediatrics who will make final decision on the appointments are: Dr. James G. Hughes, Chairman; Dr. Henry Poncher and Dr. Robert Lawson.

Those interested in applying may correspond with Dr. James G. Hughes, Le Bonheur Children's Hospital, Adams and Dunlap, Memphis, Tenn., and will receive application forms.

* * *

It is proposed that a Symposium on Child Health in the Tropics should be held in Jamaica immediately after the International Pediatric Congress. This is to be held at the University College of the West Indies, Mona, St. Andrew, Jamaica.

The provisional agenda includes the following sections: (A) Nutrition; (B) Liver Diseases; (C) Food Poisoning in the Tropics; (D) Infectious and Parasitic Diseases; (E) Prenatal and Neonatal Paediatrics; (F) Organizations of Child Health Work in Underdeveloped Areas; (G) Miscellaneous.

As accommodation is limited, those wishing to attend are asked to communicate with the provisional committee as soon as possible, sending preliminary notes on the papers they would care to present. Papers should be in English.

Communications should be addressed to: The Secretaries, Symposium on Child Health, Division of Medicine, University College of the West Indies, Jamaica, B.W.I.

* * *

The Pediatric Staff of the Cook County Hospital announces that the Fifth Annual Morris Lamm Blatt Memorial Fund lectures will be given Monday, Oct. 26, 1953, in conjunction with the Julian Levinson Research Foundation. Dr. Milton G. Bohrod, Director of the Clinical and Pathological Laboratories at the Rochester General Hospital, Rochester, N.Y., will speak on "Pathology of Allergy." The lecture will be presented at 8:30 P.M. in the Medical Amphitheatre of the Cook County Hospital.

* * *

The following pediatricians have been certified in the sub-specialty of Pediatric Allergy at the examination held in Chicago on April 28, 1953:

Percy Hall Jennings, Jr., M.D., Berkeley Pediatric Group, 1650 Walnut St., Berkeley, Calif.
Maurice Kaufman, M.D., 180 Market St., Lexington, Ky.
Carroll M. Pounders, M.D., 504 Osler Bldg., 1220 N. Walker Ave., Oklahoma City
Walker L. Rucks, M.D., 1073 Madison Ave., Memphis

The following diplomates were certified by the American Board of Pediatrics, Inc.:
Baltimore—Feb. 20, 21 and 22, 1953

Abelman, Lester M., 201 Lexington St., Belmont, Mass.
Apt, Leonard, Children's Medical Center, 300 Longwood Ave., Boston
Arnold, Gayle Gardner, 414 W. Franklin St., Richmond, Va.
Ashbey, Dwight Ransford, Jr., 237 E. Orange St., Lancaster, Pa.
Balakrishnan, Subrahmanya, Room 449, Central Y.M.C.A., 40 College St., Toronto
Bass, Lee Weil, Children's Hospital, Pittsburgh
Bauman, William Allen, 101 Cooper Drive, New Rochelle, N.Y.
Benbow, Edward P., Jr., 371 N. Elm St., Greensboro, N.C.
Blatt, Norman H., 3026 S. California Ave., Chicago
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MEMPHIS—Mar. 27, 28 and 29, 1953

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Wright, Sam Martin, 1421 Third Ave., S.W., Rochester, Minn.

* * *

Dr. Alfred L. Kastner, Milwaukee, died on April 5, 1953. He was a Fellow of the American Academy of Pediatrics.

* * *

Dr. Earl W. May, Highland Park, Mich., and East Grand Lake, Alpena, Mich., died on Dec. 16, 1952. He was an Emeritus member of the American Academy of Pediatrics.

BOOK REVIEWS

ANNUAL REVIEW OF MEDICINE, edited by Windsor C. Cutting, M.D., Stanford, Calif., Annual Reviews, Inc., 1952, $6.00, 442 pp.

A compilation of selected articles prepared individually on current topics varying widely in subject matter. The material is prepared for use by the internist, not the specialist in the field reviewed. It is recommended also for use of pediatricians in a considerable degree. The form of presentation is excellent. Contents include the following titles and authors: Infectious Diseases, W. S. Tillett; Diseases of the Gastrointestinal Tract, G. Cheney; Diseases of the Cardiovascular System, R. J. Bing; Diseases of the Urinary System, F. Hinman, Jr.; Diseases of the Reticuloendothelial System and Hematology, L. Whitby; Nutrition and Nutritional Diseases, D. P. Cuthbertson; Endocrinology, E. M. MacKay; Allergy, J. Ferrebee; Neoplastic Diseases, G. B. Mider; Diseases of the Reproductive System, C. F. Fluhmann; Diseases of the Nervous System, R. Adams; Psychiatry, T. A. C. Rennie; Diseases of the Respiratory System, L. F. Davenport; Physical Agents and Trauma, H. N. Harkins; Radiology, M. H. Wittenborg; Diseases of Bones and Joints, J. H. Bauer; Obstetrics, F. F. Snyder; Tropical Diseases, E. W. Dennis and D. A. Berberian; Plastic Surgery, L. T. Byars and P. Randall; Annotated List of Reviews in Medicine, E. M. MacKay.

PERSONALITY IN THE MAKING, edited by Helen Witmer and Ruth Katinsky, New York, Harper & Brothers, 1952, $4.50, 454 pp.

This is the official report which in its own words "summarizes for a nation wide audience" the important findings of the studies of the Midcentury White House Conference on Children and Youth. The members of the committee which prepared this report were drawn from the fields of education, health, law, philosophy, psychology, religion, social work and the social sciences.

This volume is a valuable and rich addition to the pediatrician's library. It gives in comprehensive and practical form the facts and opinions which represent our present knowledge in relation to healthy personality development, and yet it is not guilty of oversimplifying a complex subject. It distinguishes between fact and opinion and makes clear the need for further research.

The volume is arranged in 2 parts: part 1 which is on the development of the healthy personality and part 2 on implications for the conduct of social institutions.

This is one book which lives up to the "blurbs" on the cover. It is strongly recommended to all persons who are interested in children.

ELECTROCARDIOGRAPHIC STUDIES IN NORMAL INFANTS AND CHILDREN, R. F. Ziegler, Springfield, Ill., Charles C Thomas, Publisher, 1951, $10.50, 195 pp., 297 illustrations.

This book fills a gap of the current literature, because the lack of adequate standards in electrocardiography of normal infants and children is the cause of questionable and often incorrect interpretation of many tracings. Differentiation between normal and abnormal tracings of children is undoubtedly difficult in most cases.

Reviewing the present literature, the author concludes that the form of the ventricular deflections in infants and children has never been satisfactorily explained. There are different opinions as to whether right axis deviation is due to the position of the heart to the prevalence of the right ventricle.

The present study is based on electrocardiograms of normal subjects from birth to 16 years. In the first series of 250 children, the precordial leads were excluded because of technical errors. In the second series of 300, a complete study was made including standard and unipolar limb leads, and 6 precordial leads (V1 to V6). In an additional series of 85, V4R and VE leads were also recorded.

The importance of a proper technic is emphasized. Correct tension of the string, special care in placing the electrodes on the chest, and use of a smaller electrode (1.5 cm. diameter) are required. Excess of electrode jelly is a frequent source of technical errors, causing collection of electric potentials from a larger surface of the chest; then, a constant pattern occurs and an inverted T-wave is found in all chest leads including V5 and V6.

Normal heart rate for the various ages is presented in table form. Besides the sinus tachycardia commonly observed in infants, 2 instances, one of sinus bradicardia and one of complete heart block without evidence of organic heart disease, are illustrated. The incidence and degree of sinus arrhythmia increase with age and in proportion with the decreasing heart rate; this fact is of clinical value in the correct interpretation of ECGs, e.g., in active rheumatic carditis. Paroxysmal auricular flutter was encountered once, and supraventricular premature contractions were also observed in a normal child. It is possible that routine ECGs in the neonatal period would show a higher incidence of disturbances of the heart rate.

The duration, amplitude and direction of P-wave were measured. The duration was found greater on the left side of the chest and increasing with age, probably due to increasing length of auricular bundles. The electric axis of P ranged from 45° to 60° and there was no correlation between mean electric axis of P and either age or mean electric axis of QRS. This supports the concept that, in normal hearts, the axis of P is mostly related to the average direction of the auricular activation as determined by the location of the cardiac pacemaker.

Particular attention was paid to correct measurement of the PR interval, through subtraction of the maximum QRS interval from the maximum P-S interval in any lead. Figures of average values for each age group are given.

The QRS interval was found increasing with age; however, at birth this interval was slightly longer than at 1 week of age. A precordial pattern of complete right bundle branch block was observed in 6.5% of the normal infants or children included in the present study; left bundle branch block was never observed.

The QT interval and the duration of T were measured according to Bazett's formula.

The average mean electric axis of QRS was calculated by several different methods; it is apparent that there is a gradual change of position of the heart from approximately +120° in the neonatal period to between +60° and +90° at the age of 6 months; then, a stable pattern which lasts during childhood is reached. The influence of right ventricular hypertrophy on the electric position of the heart is pointed out; this can explain the noncoincidence between anatomic and electric position of the heart in infancy and childhood.

In 3 infants below 6 months of age, unexplained Q-wave was observed on the right side of the chest.

The amplitude of Q, R, and S was studied in the various ages. The S-T segment can be displaced by 0.1 mv in the limb leads, and occasionally by 0.3-0.4 mv in the chest leads.

Of particular interest are the T-wave changes of the precordial leads during the first few days of life. During the first 24 hours, the T-waves in leads from the right side of the precordium are usually upright while those from the left side are frequently inverted (they may be upright in leads from both sides, and multiphasic or inverted in leads from the midprecordium). Then the pattern changes and T becomes negative in V1 while it becomes positive in V5-V6. These changes are independent of any significant change of the QRS complex. The cause of these changes is not apparent and only theoretic possibilities may be suggested (neonatal patency of ductus arteriosus, transient anoxemia due to functional patency of foramen ovale, or early right ventricular preponderance). The average pattern of normal infants seems to be due to a single electrocardiographic vector, probably dominated at different ages by the variations of potential of either the right or the left ventricle.

The text is illustrated by tables, diagrams and ECGs. A series of representative ECGs at various ages is presented in the form of atlas. A statistical appendix of 62 pages presents in the form of diagrams and tables all the data collected. This should be useful for consultation.

The bibliography is quoted at the end of each chapter; a complete index facilitates the work of consultation.

The editorial aspect is excellent.

INDEX

Accidents, childhood, pilot study of; preliminary report (SA), 405
Acid, isonicotinic, hydrazine derivatives of, 82
ACTH and cortisone, use of; report of 3 cases of idiopathic familial hyperlipemia, 480
Adams, John M., 15
Address changes of members of Academy, 648
Adolescent girl and her menstrual problems (RTD), 70
Adrenal cortex in premature infants, function of, 120
Alexander, Hattie E., Ames, Rose G., Cohen, Sophia M., Fischer, A. E., Kohn, J., McPherson, A. Z., Marlow, Jeanette, and Rutzky, J., 323
"Alkaline" phosphatase activity, deficiency of, rickets and premature loss of teeth in childhood, 309
Allergic diseases, basic mechanisms in (S), 643
Alymphocytosis, 129
American Academy of Pediatrics, 655
  Proceedings and reports, 70, 154, 270, 393, 515, 639
  Address changes and deaths of members, 648
  Annual business meeting, summary of, 154
  Fellows elected to membership, 161
  President's address, 1
  Round Table Discussions, 70, 166, 270, 393, 515, 639
    Adolescent girl and her menstrual problems, 70
    Antibiotics, 270
    Nature, recognition and management of neuromuscular disabilities in children, 166
    Pediatric x-ray diagnosis, 639
    Problems in child psychiatry, 393
    Use of ACTH, cortisone and allied substances, 515
  Symposium, 82, 174, 280, 643
    Basic mechanisms in allergic disease, 643
    Hydrazine derivatives of isonicotinic acid, 82
    Neurological conditions in children, 174
    Surgical problems in childhood, 280
American Board of Pediatrics, diplomates certified, 304, 656
American Public Health Association, program of Committee on Child Health of, 85
American Psychiatric Association, 659
Ames, Rose G., Cohen, Sophia M., Fischer, A. E., Kohn, J., McPherson, A. Z., Marlow, Jeanette, Rutzky, J., and Alexander, Hattie E., 323
Andelman, Morton B., Perlstein, M. A., Rosner, D. C., and Wehrle, P., 628
Andersen, Dorothy H., and di Sant'Agnese, P. A., 207
Anemia, Cooley's, report of case of in Negro child; thalassemia in Negroes, 622
Anesthetic, pediatrician's responsibility when his patient is anesthetized, 549
Announcements, news and, 88, 188, 304, 423, 568, 655
Annual review of medicine (BR), 659
Arey, Stuart Lane, 140
Arnstein, Lawrence H., and Davis, J. H., 381
Aureomycin, penicillin and terramycin, comparative effects of on streptococcal tonsillitis and pharyngitis, 7

Bacillary dysentery, epidemic Shigella gastroenteritis in endemic area, 145
Bacterial viruses, chemotherapeutic aspects of studies on, 89
Bakst, Henry J., 526
Banks, L. Otto, and Scott, R. B., 622
Baumgartner, Leona, 489
BCG, vaccination par le (BR), 306
Beaver, Paul C., and Jung, R. C., 611
Bentz, Alice R., Deane, G. E., Furman, J. E., and Woodward, T. E., 368
Bessman, Samuel P., and Lucas, J. C., 109
Bill, Alexander H., Jr., 582
Biochemical differences, hitherto unrecognized, between human milk and cow's milk, 98
Blindness, incidence of gross visual defects due to retrolental fibroplasia, 238
Blood, alymphocytosis, 129
Book Reviews, 88, 306, 424, 659
  Annual review of medicine, 659
  Diagnostiche und therapeutische Technik beim Kinde (Diagnostic and therapeutic technic in pediatrics), 307
  Electrocardiographic studies in normal infants and children, 660

Études néo-natales, 307
Handbook, of pediatric medical emergencies, 88
Medical inspection of school children, 306
Personality in making, 659
Pathology of fetus and newborn, 308
Psychiatry and medical education, 659
Survey of clinical pediatrics, 424
Vaccination par le BCG, 306
Visceral innervation and its relation to personality, 307
Borges, Wayne H., Rudolph, A. M., and Nadas, A. S., 454
Boy, 7 year old, massive hydrops of gallbladder producing pyloric obstruction in, 449
Breast, galactocele in male infant, 109
Breast-fed infants in Iowa City, pattern of growth of selected groups of, 38
Buddingh, G. John, Schrum, D. I., Lanier, J. C., and Guidry, D. J., 595
Byers, Randolph K., 174

Caffey, John, 48
Calcaneus, congenital fibromyxosarcoma of os calcis, 617
Caloric insufficiency, nitrogen utilization in, 435
Canine distemper and respiratory disease of man, comparative study of, 15
Carbohydrate, added, renal water requirement of infants fed evaporated milk with and without, 65
Celiac disease,
1. Mode of onset and diagnosis, 207
2. Course and prognosis, 224
Chemotherapeutic aspects of studies on bacterial viruses, 89
Chest, funnel; indications for surgery and time of choice for operation, 582
Child health conference, use of in training medical students, 538
Magnuson Commission recommendations for, 286
psychiatry, problems in (RTD), 393
Childhood accidents, pilot study of; preliminary report (SA), 405
rickets, deficiency of "alkaline" phosphatase activity and premature loss of teeth in, 309
surgical problems in (S), 280
Children, effect of magnesium sulfate on renal dynamics in acute glomerulonephritis in, 191
nature, recognition and management of neuromuscular disabilities in (RTD), 166
neurological conditions in (S), 174
ovarian maturation and cyst formation in, 588
school, medical inspection of (BR), 306
with "collagen diseases," serum complement in, 569
young, infants and, eosinophilia-hepatomegaly syndrome of; report of case due to invasion of liver by nematode larvae, 358
Chloromycetin palmitate®; treatment of meningitis with; results of therapy in 23 cases, 368
Clark, Leland C., Jr., Sobel, Edna H., Fox, R. Phyllis, and Robinow, M., 309
Coe, Herbert E., 280
Cohen, Seymour S., 89
Cohen, Sophia M., Ames, Rose G., Fischer, A. E., Kohn, J., McPherson, A. Z., Marlow, Jeanette, Rutzky, J., and Alexander, Hattie E., 323
"Collagen diseases," serum complement in children with, 569
Committee on Child Health of American Public Health Association, program of, 85
Committee on Rheumatic Fever and Cardiac Disease, American Academy of Pediatrics, 88
Conference, health, child, use of in training of medical students, 538
Congenital dislocation of hip, 28
heart disease, cyanotic, hematologic adjustments to, 454
fibromyxosarcoma of os calcis, 617
Convulsions, febrile, significance of, 341
Cook County Graduate School of Medicine, 304, 568
Cook County Hospital, 655
Cooley's anemia, report of case of in Negro child; thalassemia in Negroes, 622
Cortex, adrenal, in premature infants, function of, 120
Cortisone, ACTH and, use of; report of 3 cases of idiopathic familial hyperlipemia, 480
Cow's milk, human milk and, hitherto unrecognized biochemical difference between, 98
Cox, Warren M., Jr., Ellingson, R. C., and Mueller, A. J., 435
Coxsackie viruses, group A, herpangina:clinical and laboratory aspects of outbreak caused by, 113
Cutting, Windsor C., 659
Cyanotic congenital heart disease, hematologic adjustments to, 454

Cyst formation, ovarian maturation and, in children, 588
galactocele in male infant, 109
Cysts, pulmonary, on natural regression of during early infancy, 48
Cytomegalic inclusion disease, generalized, clinical diagnosis of, 502

Davis, Joseph H., and Arnstein, L. H., 381
Deafness, hearing test for newborn infants, 634
Deane, Garrett E., Furman, J. E., Bentz, Alice R., and Woodward, T. E., 368
Dearing, W. Palmer, 285
Deisher, Robert W., 538
DeMaria, William J. A., and Harris, J. S., 191
Denny, Floyd W., Wannamaker, L. W., and Hahn, E. O., 7
DeSanctis, Adolph G., and Varga, C., 88
Diarrhea, early history of fluid replacement therapy, 554
Di Sant'Agnese, Paul A., 207
and Andersen, Dorothy H., 207
Diabetes insipidus, dominant inheritance of; family study, 238
Diabetes, transient, in infancy, 140
Diagnosis, clinical, of endocardial fibrosis; analysis of literature with report of four new cases, 255
x-ray, pediatric (RTD), 639
Diagnostiche und therapeutische Technik beim Kinde (Diagnostic and therapeutic technic in pediatrics) (BR), 306
Diarrhea, epidemic Shigella gastroenteritis (bacillary dysentery) in endemic area, 145
Diphenan®, egressin® and gentian violet, treatment of enterobiasis (pinworm infestation) with, 611
Disabilities, neuromuscular, in children, nature, recognition and management of (RTD), 166
Dislocation of hip, congenital, 28
Distemper, canine, and respiratory disease of man, comparative study of, 15
Dog, comparative study of canine distemper and respiratory disease of man, 15
Donohue, W. L., 129
Dorfman, Albert, 515
Domiciliary medical care and voluntary teaching hospital, 526
Drugs, international non-proprietary names for drugs, 290
Dysentery, bacillary, epidemic Shigella gastroenteritis in endemic area, 145

Economic value of preventive medicine, 544
Editorial, 189
Education, medical, psychiatry and (BR), 659
Egressin®, diphenan® and gentian violet, treatment of enterobiasis (pinworm infestation) with, 611
Electrocardiagraphic studies in normal infants and children (BR), 660
Ellingson, Rudolph C., Cox, W. M., Jr., and Mueller, A. G., 435
Emergencies, medical, pediatric, handbook of (BR), 88
Empyema, staphylococcal pneumonia and, 385
Encephalitis, measles, 473
Endocardial fibrosis, clinical diagnosis of; analysis of literature with report of four new cases, 255
Englender, Gail S., and Lee, C. M., Jr., 449
Enterobiasis (pinworm infestation), treatment of with diphenan®, egressin® and gentian violet, treatment of, 611
Eosinophilia-hepatomegaly syndrome of infants and young children; report of case due to invasion of liver by nematode larvae, 358
Epidemic Shigella gastroenteritis (bacillary dysentery) in endemic area, 145
Epstein, Bernard, Kanof, A., Kramer, B., and Mauss, I., 385
Ernst, Kenneth F., and Milburn, C. L., Jr., 358
Études néo-natales (BR), 306
Evaporated milk with and without added carbohydrate, renal water requirement of infants fed, 65
Eye, incidence of gross defects due to retrolental fibroplasia, 238

Febrile convulsions, significance of, 341
Feig, Milton, 145
Fetus and newborn, pathology of (BR), 308
Fibroelastosis, endocardial—*See* Endocardial fibrosis
Fibromyxosarcoma, congenital, of os calcis, 617
Fibroplasia, retrolental, incidence of gross visual defects due to, 238
Fibrosis, endocardial, clinical diagnosis of; analysis of literature with report of 4 new cases, 255
Fischer, A. E., Ames, Rose G., Cohen, Sophia M., Kohn, J., McPherson, A. Z., Marlow, Jeanette, Rutzky, J., and Alexander, Hattie E., 323
Fluid replacement therapy, early history of, 554
Fluoroscopes, shoe-fitting, 189
Fox, R. Phyllis, Sobel, Edna H., Clark, L. C., Jr., and Robinow, M., 309

Fraser F. Clarke, and Pender, C. B., 246
Funnel chest; indications for surgery and time of choice for operation, 582
Furman, J. Earle, Deane, G. E., Bentz, Alice R., and Woodward, T. E., 368

Galactocele in male infant, 109
Gallbladder, massive hydrops of, producing pyloric obstruction in 7 year old boy, 449
Gamble, James L., 554
Gaskins, Albert L., Scott, R. B., and Kessler, Althea D., 480
Gastroenteritis, Shigella, epidemic (bacillary dysentery), in endemic area, 145
Genn, Minnie Marder, Langford, W. S., Gilder, R., Jr., Wilking, Virginia N., and Sherrill, Helen H., 405
Gentian violet, diphenan®, and egressin®, treatment of enterobiasis (pinworm infestation) with, 611
Gilder, Rodman, Jr., Langford, W. S., Wilking, Virginia N., Genn, Minnie Marder and Sherrill, Helen H., 405
Gingivostomatitis, studies of natural history of herpes simplex infections, 595
Girl, adolescent, and her menstrual problems (RTD), 70
Gland, adrenal, function of adrenal cortex in premature infants, 120
salivary, clinical diagnosis of generalized cytomegalic inclusion disease, 502
Glomerulonephritis, acute, effect of magnesium sulfate on renal dynamics in in children, 191
Great Britain, National Health Service in, 179
Grossman, Herbert J., Richmond, J. B., and Lustman, S. L., 634
Growth of selected groups of breast-fed infants in Iowa City, pattern of, 38
Guidry, D. Joseph, Buddingh, G. J., Schrum, D. I., and Lanier, J. C., 595
Guyton, Donald H., Mercer, R. D., and Luse, Sarah, 502
György, Paul, 98

Hahn, Edward O., Denny, F. W., and Wannamaker, L. W., 7
Handbook of pediatric medical education (BR), 88
Harper, Charles L., Jr., Holmes, E. M., Jr., and Nelson, K., 531
Harper, Paul A., 179, 284, 416, 525
Harris, Jerome S., and DeMaria, William J. A., 191
Harvard Medical School, 88
Health, child, Magnuson Commission recommendations for, 286
conference, child, use of in training of medical students, 538
public, aspects of problems of current interest in neonatal pediatrics, 489
nursing and medical social work, 290, 652
Hearing test for newborn infants, 634
Heart, clinical diagnosis of endocardial fibrosis; analysis of literature with report of four new cases, 255
disease, congenital, cyanotic, hematologic adjustments to, 454
Heel bone, congenital fibromyxosarcoma of os calcis, 617
Hematologic adjustments to cyanotic congenital heart disease, 454
Hepatomegaly, eosinophilia-, syndrome of infants and young children; report of case due to invasion of liver by nematode larvae, 358
Herpangina: clinical and laboratory aspects of outbreak caused by group A Coxsackie viruses, 113
Herpes, simplex infections, studies of natural history of, 595
Hess, Julius H., 425
Hip, congenital dislocation of, 28
Holmes, E. M., Jr., Nelson, K., and Harper, C. L., Jr., 531
Home medical care program, Richmond, 531
Hospital, teaching, voluntary, domiciliary medical care and, 526
Hubbard, John P., 85, 286, 419, 538
Huët, A., and Mande, R., 306
Hummeler, Klaus, Kravis, Lillian P., Sigel, M. M., and Lecks, H. I., 113
Hydrazine derivatives of isonicotinic acid (S), 82
Hydrops of gallbladder, massive, producing pyloric obstruction in 7 year old boy, 449
Hyperlipemia, familial, idiopathic, report of 3 cases of: use of ACTH and cortisone, 480
Hypertension in poliomyelitis, incidence of, 628

Idiopathic celiac disease.
I. Mode of onset and diagnosis, 207
II. Course and prognosis, 224
Infancy, early, on natural regression of pulmonary cysts during, 48
transient diabetes in, 140
Infant, male, galactocele in, 109

Infants, breast-fed, in Iowa City, pattern of growth of selected groups of, 38
fed evaporated milk with and without added carbohydrate, renal water requirement of, 65
newborn, hearing test for, 634
premature, function of adrenal cortex in, 120
prematurely born, experiences gained in 30 year study of, 425
Infants and children, normal, electrocardiographic studies in (BR), 660
young children, eosinophilia-hepatomegaly syndrome of; report of case due to invasion of liver by nematode larvae, 358
Infections, herpes simplex, studies of natural history of, 595
Inoue, Tetsuji, and Wright, Phyllis M., 465
International non-proprietary names for drugs, 290
Iowa City, pattern of growth of selected groups of breast-fed infants in, 38
Isonicotinic acid, hydrazine derivatives of, 82

Janeway, Charles A., and Wedgwood, R. J. P., 569
Jung, Rodney C., and Beaver, P. C., 611

Kanner, Leo, 393
Kanof, Abram, Epstein, B., Kramer, B., and Mauss, I., 385
Kastner, Alfred L., 658
Kessler, Althea D., Gaskins, A. L., and Scott, R. B., 480
Kidney, effect of magnesium sulfate on renal dynamics in acute glomerulonephritis in children, 191
renal water requirement of infants fed evaporated milk with and without added carbohydrate, 65
Kohn, J., Ames, Rose G., Cohen, Sophia M., Fischer, A. E., McPherson, A. Z., Marlow, Jeanette, Rutzky, J., and Alexander, Hattie, E., 323
Kramer, Benjamin, Kanof, A., Epstein, B., and Mauss, I., 385
Kravis, Lillian P., Hummeler, K., Sigel, M. M., and Lecks, H. I., 113
Kuntz, Albert, 307

Lambert, Edward C., Shumway, Clare N., and Terplan, K., 255
Langford, William S., Gilder, R., Jr., Wilking, Virginia N., Genn, Minnie Marder, and Sherrill, Helen H., 405
Lanier, James C., Buddingh, G. J., Schrum, D. I., and Guidry, D. J., 595
Lanman, Jonathan T., 120
Larvae, nematode, report of case due to invasion of liver by; eosinophilia-hepatomegaly syndrome of infants and young children, 358
Lecks, Harold I., Kravis, Lillian P., Hummeler, K., and Sigel, M. M., 113
Lee, C. Marshall, Jr., and Englender, Gail S., 449
Lennox, William G., 341
Liver, invasion of by nematode larvae, report of case due to; eosinophilia-hepatomegaly syndrome of infants and young children, 358
Lucas, John C., and Bessman, S. P., 109
Luse, Sarah, Mercer, R. D., and Guyton, D. H., 502
Lustman, Seymour L., Richmond, J. B., and Grossman, H. J., 634
Lymphocytes, alymphocytosis, 129

McArthur, Janet W., 70
McCaffrey, Isabel, and Schlesinger, E. R., 238
McIntyre, Ross A., and Oberst, B. B., 338
McPherson, A. Z., Ames, Rose G., Cohen, Sophia M., Fischer, A. E., Kohn, J., Marlow, Jeanette, Rutzky, J., and Alexander, Hattie E., 323
Magnesium sulfate, effect of on renal dynamics in acute glomerulonephritis in children, 191
Magnuson Commission recommendations for child health, 286
Mammary gland, galactocele in male infant, 109
Man, canine distemper and respiratory disease of, comparative study of, 15
Mande, R., and Huët, A., 306
Markman, Charles A., Solomons, G., and West, E. J., 473
Marlow, Jeanette, Ames, Rose G., Cohen, Sophia M., Fischer, A. E., Kohn, J., McPherson, A. Z., Rutzky, J., and Alexander, Hattie E., 323
Martin, Walter B., 418
Massachusetts General Hospital, 304
Mauss, Irving, Kanof, A., Epstein, B., and Kramer, B., 385
May, Earl W., 658
Measles encephalitis, 475
Medical care, domiciliary, and voluntary teaching hospital, 526
program, home, Richmond, 531

education, psychiatry and (BR), 659
emergencies, pediatric, handbook of (BR), 88
inspection of school children (BR), 306
social work, public health and nursing, 290, 652
students, training of, use of child health conference in, 538
Medicine, annual review of (BR), 659
preventive, economic value of, 544
Memorial Center for Cancer and Allied Diseases, 423
Meningitis, treatment of with chloromycetin palmitate®; results of therapy in 23 cases, 368
Menstrual problems, her, adolescent girl and (RTD), 70
Mercer, Robert D., Luse, Sarah, and Guyton, D. H., 502
Milburn, Conn L., Jr., and Ernst, K. F., 358
Milk, cow's, human milk and, hitherto unrecognized biochemical difference between, 98
evaporated, with and without added carbohydrate, renal water requirement of infants fed, 65
human, and cow's milk, hitherto unrecognized biochemical difference between, 98
pattern of growth of selected groups of breast-fed infants in Iowa City, 38
Miller, Robert W., 294
Mueller, A. J., Cox, W. M., Jr., and Ellingson, R. C., 435

Nadas, Alexander, S., Rudolph, A. M., and Borges, W. H., 454
National Health Service of Great Britain, 179
Negroes, thalassemia in; report of case of Cooley's anemia in Negro child, 622
Nelson, Kinloch, Holmes, E. M., Jr., and Harper, C. L., Jr., 531
Nematode larvae, report of case due to invasion of liver by; eosinophilia-hepatomegaly syndrome of infants and young children, 358
Neonatal pediatrics, public health aspects of problems of current interest in, 489
Neo-natal studies (études néo-natales) (BR), 306
Nerves, visceral innervation and its relation to personality (BR), 306
Neter, Erwin, 270
Neuhauser, Edward B. D., 639
Neurological conditions in children (S), 174
Neuromuscular disabilities in children, nature, recognition and management of (RTD), 166
Newborn, pathology of fetus and (BR), 308
News and announcements, 88, 188, 304, 423, 568, 655
Nicotine poisoning, acute; case report, 338
Nitrogen utilization in caloric insufficiency, 435
Nitsch, Kurt, 307
Nursing, public health and medical social work, 290, 652

Oberst, Byron B., and McIntyre, R. A., 338
Os calcis, congenital fibromyxosarcoma of, 617
Ovarian maturation and cyst formation in children, 588

Paiva, Silvio L., 38
Pathology of fetus and newborn (BR), 308
Patient, pediatrician's responsibility when his is anesthetized, 549
Pediatric allergy, sub-specialty of, pediatricians certified, 568, 655
medical emergencies, handbook of (BR), 88
research, year of progress in supported by Playtex Park Research Institute, 419
x-ray diagnosis (RTD), 639
Pediatrician and public, 179, 284, 416, 525
Pediatrician's responsibility when his patient is anesthetized, 549
Pediatrics, clinical, survey of (BR), 424
diagnostic and therapeutic technic in (diagnostiche und therapeutische Technik beim Kinde) (BR), 306
neonatal, public health aspects of problems of current interest in, 489
some potential hazards of use of roentgen rays in (SR), 294
Pender, C. B., and Fraser, F. C., 246
Penicillin, aureomycin and terramycin, comparative effects of on streptococcal tonsillitis and pharyngitis, 7
Perlstein, Meyer A., 166
Andelman, M. B., Rosner, D. C., and Wehrle, P., 628
Personality in making (BR), 659
visceral innervation and its relation to (BR), 306
Pertussis, comparison of therapeutic efficacy of four agents in, 323
Peterson, Osler L., 179
Pharyngitis, streptococcal tonsillitis and, com-

parative effects of penicillin, aureomycin and terramycin on, 7
Phosphatase, "alkaline," activity, deficiency of, rickets and premature loss of teeth in childhood, 309
Pilot study of childhood accidents; preliminary report (SA), 405
Pinworm infestation, treatment of enterobiasis with diphenan®, egressin® and gentian violet, 611
Playtex Park Research Institute, year of progress in pediatric research supported by, 419
Plummer, George W., 28
Pneumonia, staphylococcal, and empyema, 385
Poisoning, nicotine, acute; case report, 338
Polhemus, Donald W., 588
Poliomyelitis, incidence of hypertension in, 628
Potter, Edith L., 308
Pratt, Edward L., and Snyderman, Selma E., 65
President's address, American Academy of Pediatrics, 1
Preventive medicine, economic value of, 544
Program, Richmond home medical care, 531
Psychiatry and medical education (BR), 659
child, problems in (RTD), 393
Public health aspects of problems of current interest in neonatal pediatrics, 489
nursing and medical social work, 290, 652
pediatrician and, 179, 284, 416, 525
Pulmonary cysts, on natural regression of during early infancy, 48
Pyloric obstruction in 7 year old boy, massive hydrops of gallbladder producing, 449

Quillian, Warren W., 1

Ratner, Bret, 82, 643
Rays, roentgen, some potential hazards of use of in pediatrics, 294
Renal dynamics, effect of magnesium sulfate on in acute glomerulonephritis in children, 191
water requirement of infants fed evaporated milk with and without added carbohydrate, 65
Research, pediatric, year of progress in supported by Playtex Park Research Institute, 419
Respiratory disease of man, canine distemper and, comparative study of, 15
Retrolental fibroplasia, incidence of gross visual defects due to, 238
Richmond home medical care program, 531
Richmond, Julius B., Grossman, H. J., and Lustman, S. L., 634
Rickets, deficiency of "alkaline" phosphatase activity and premature loss of teeth in childhood, 309
Robinow, Meinhard, Sobel, Edna H., Clark, L. C., Jr., and Fox, R. Phyllis, 309
Roentgen rays in pediatrics, some potential hazards of use of (SR), 294
Rogers, Kenneth D., and Wishik, S. M., 549
Rosner, David C., Perlstein, M. A., Andelman, M. B., and Wehrle, P., 628
Round Table Discussion, 70, 166, 270, 393, 515, 639
Adolescent girl and her menstrual problems, 70
Antibiotics, 270
Nature, recognition and management of neuromuscular disabilities in children, 166
Pediatric x-ray diagnosis, 639
Problems in child psychiatry, 393
Use of ACTH, cortisone and allied substances, 515
Rudolph, Abraham M., Nadas, A. S., and Borges, W. H., 454
Rutzky, J., Ames, Rose G., Cohen, Sophia M., Fischer, A. E., Kohn, J., McPherson, A. Z., Marlow, Jeanette, and Alexander, Hattie E., 323

St. Christopher's Hospital for Children, 423
Sclerosis, endocardial—*See* Endocardial fibrosis
Schlesinger, Edward R., and McCaffrey, Isabel, 238
School children, medical inspection of (BR), 306
Schrum, David I., Buddingh, G. J., Lanier, J. C., and Guidry, D. J., 595
Scott, Roland B., and Banks, L. O., 622
Gaskins, A. L., and Kessler, Althea D., 480
Section on Pediatrics, American Medical Association, 568
Serum complement in children with "collagen diseases," 569
Sherrill, Helen H., Langford, W. S., Gilder, R., Jr., Wilking, Virginia N., and Genn, Minnie Marder, 405
Shigella gastroenteritis (bacillary dysentery), epidemic, in endemic area, 145
Shoe-fitting fluoroscopes, 189
Shumway, Clare N., Lambert, E. C., and Terplan, K., 255
Sigel, M. Michael, Kravis, Lillian P., Hummeler, K., and Lecks, H. I., 113
Skin, studies of natural history of herpes simplex infections, 595

Slavens, John J., 617
Slobody, Lawrence B., 424
Snyderman, Selma E., and Pratt, E. L., 65
Sobel, Edna H., Clark, L. C., Jr., Fox, R. Phyllis, and Robinow, M., 309
Social work, medical, public health and nursing, 290, 652
Solomons, Gerald, Markman, C. A., and West, E. J., 473
Special Article, 405
Special Reviews, 294
Some potential hazards of use of roentgen rays in pediatrics, 294
Special Sections, 85, 179, 284, 416, 525, 652
Staphylococcal pneumonia and empyema, 385
Stokes, Joseph, Jr., 294, 549
Streptococcal tonsillitis and pharyngitis, comparative effects of penicillin, aureomycin and terramycin on, 7
Surgery, indications for, and time of choice for operation; funnel chest, 582
Surgical problems in childhood (S), 280
Survey of clinical pediatrics (BR), 424
Syphilis, third-generation; report of probable case, 465
Symposium, 82, 174, 643
Basic mechanisms in allergic diseases, 643
Hydrazine derivatives of isonicotinic acid, 82
Neurological conditions in children, 174
Surgical problems in childhood, 280

Teaching hospital, voluntary, domiciliary medical care and, 526
Teeth, premature loss of, rickets, deficiency of "alkaline" phosphatase activity and in childhood, 309
Terplan, Kornel, Lambert, E. C., and Shumway, Clare N., 255
Terramycin, penicillin and aureomycin, comparative effects of on streptococcal tonsillitis and pharyngitis, 7
Test, hearing, for newborn infants, 634
Thalassemia in Negroes; report of case of Cooley's anemia in Negro child, 622
Thirst, dominant inheritance of diabetes insipidus; family study, 238
Tonsillitis, streptococcal, and pharyngitis, comparative effects of penicillin, aureomycin and terramycin on, 7
Trends, 85, 286, 419
Tulane Medical School, 88
Tumor, congenital fibromyxosarcoma of os calcis, 617

University of California School of Medicine, 568
University College of the West Indies, 655
University of Utah, 304

Vaccination par le BCG (BR), 306
Varga, Charles, and DeSanctis, A. G., 88
Viruses, bacterial, chemotherapeutic aspects of studies on, 89
Coxsackie, group A, herpangina: clinical and laboratory aspects of outbreak caused by, 113
Visceral innervation and its relation to personality (BR), 306
Visual defects, gross, incidence of due to retrolental fibroplasia, 238

Wannamaker, Lewis W., Denny, F. W., and Hahn, E. O., 7
Wedgwood, Ralph J. P., and Janeway, C. A., 569
Wegman, Myron E., 290, 544, 652
Wehrle, Paul, Perlstein, M. A., Andelman, M. B., and Rosner, D. C., 628
West, Edward J., Solomons, G., and Markman, C. A., 473
Wilking, Virginia N., Langford, W. S., Gilder, R., Jr., Genn, Minnie Marder, and Sherrill, Helen H., 405
Wilkins, Edgar Henry, 306
Wishik, Samuel M., 85
and Rogers, K. D., 549
Witmer, Helen, and Katinsky, Ruth, 659
Woodward, Theodore E., Deane, G. E., Furman, J. E., and Bentz, Alice R., 368
Wright, Phyllis M., and Inoue, T., 465

X-rays, some potential hazards of use of roentgen rays in pediatrics (SR), 294
diagnosis, pediatric (RTD), 639.

Ziegler, R. F., 660